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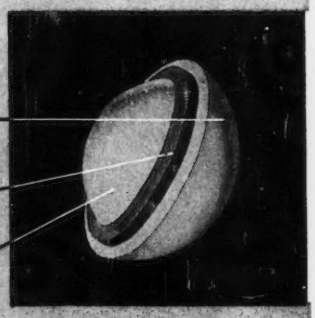

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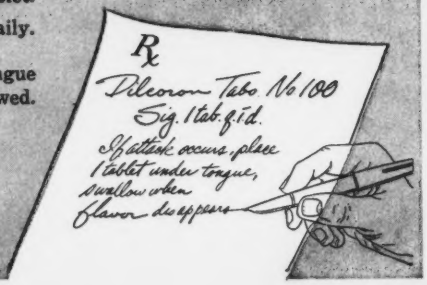

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HERRMAN L. BLUMGART, M.D., *Editor-in-Chief*
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Editorial

Iproniazid and Angina Pectoris

IT SEEMS apparent that iproniazid is capable of alleviating many of the symptoms of the anginal syndrome in a significant number of patients. It has been reported that several patients with intractable angina pectoris have been dramatically relieved after institution of iproniazid therapy.

Some of the early papers reported that electrocardiograms indicated reversal or improvement of the coronary vascular pathology when compared with pretreatment electrocardiograms. Subsequent investigations have failed to confirm these findings.

The mechanism of action in regard to the myocardial effects of iproniazid are purely speculative. Most investigators postulate that a combination of central nervous system, psychic, and autonomic effects, as well as peripheral monamine-oxidase inhibition actions, are involved. The myocardial action may be related to accumulation of serotonin, or sympathomimetic amines, or both, and their metabolites with resulting coronary dilatation.

It is imperative in therapy of coronary vascular disease that the clinician consider carefully all aspects and all potential ramifications of such therapy. If the subjective relief of pain occurring in the patients receiving iproniazid is not due to specific reversal of the primary pathologic lesion, then not only is the cardiac alarm system disrupted, but the manifest stimulant and euphoriant properties of iproniazid are responsible for an increased demand on an already embarrassed circulation. Even if the drug does influence the pathologic process favorably, the central nervous system stimulation resulting in an increase in motor and sensory activity and the pronounced euphoria with concomitant reduced feeling of need for restriction of activity must be regarded as relative contraindications for the use of such a drug.

It is very difficult to divorce the expected pharmacologic actions of this agent from what are regarded as adverse reactions. For example, degree of stimulation is dose-related but not predictable and is not infrequently excessive, even with relatively small doses. The untoward reactions associated with central nervous system stimulation include: restlessness, palpitation, insomnia, hyperreflexia, tingling of extremities, muscle twitching, and clonus. Some signs and symptoms specifically associated with stimulation of the autonomic nervous system include constipation, dryness of the mouth, diaphoresis, and frequency and delay in micturition. Side reactions probably associated with central nervous system actions but not usually classified as stimulant in nature include: euphoria, psychotic reactions, dyspnea, impotence, and hypotensive reactions. Miscellaneous side reactions, not related to the recognized pharmacologic activity of the drug, include edema, drowsiness, mild anemia, vertigo, tinnitus, and hepatotoxicity.

Of the side reactions listed above, one which should cause marked concern because of its unpredictability is the hypotensive response. Acute hypotension does occur in patients receiving iproniazid. Such episodes are most often associated with doses of 150 mg. or more per day. They are presumably not common

and rarely severe in dosages of less than 50 mg. per day. This particular effect should be given special consideration in this discussion, since an acute fall in blood pressure in a patient with coronary vascular disease may be a very serious complication.

The preceding effects that are associated with iproniazid therapy are, for the most part, as indicated previously, dose-related. However, stimulant effects on the central nervous system do occur following doses of 50 mg. per day. Likewise autonomic nervous system effects, even though compensated, occur as a result of use of this agent at the 50-mg. dose level. The untoward reactions, which are fairly frequent complications of therapy, present particular hazards when they occur in patients with coronary vascular disease. For these reasons even without consideration of the hepatotoxic aspect it has been the opinion of the majority of investigators, shared by the clinical staff of Hoffmann-La-Roche, that iproniazid should not be employed in the routine treatment of angina pectoris except possibly in those instances in which the syndrome has progressed to the severe intractable stage. We believe that this impression would apply equally to the 50-mg. per day and 150-mg. per day dosage schedules.

Iproniazid was first recommended for use in mental illness associated with depression in April 1957. It was only when the drug was introduced into this very much expanded clinical area that the association of this agent with hepatitis was definitely recognized. Owing to the very close resemblance of this disease, both clinically and pathologically, to infectious hepatitis the now accepted cause and effect relationship could not be established immediately.

The Food and Drug Administration was first made aware of this situation by the drug manufacturer, Hoffmann-LaRoche, in February 1958. The firm indicated that they were making every effort to advise physicians of the potential hazard and were in the process of intensive investigation of this problem, the results of which they would report to us at given intervals. We reviewed the information that they had available at that time, including 64 reports of hepatitis associated with iproniazid therapy and resulting in 15 deaths. The incidence of jaundice was calculated to be approximately 1 per 4,000 patients treated. More than 22 per cent of the patients who were afflicted with hepatitis succumbed. Because of the uniqueness of the central stimulant properties of iproniazid, and because of its potential importance as a therapeutic tool in the treatment of mental illness with associated depression, and in consideration of the inconclusive nature of the available reports, a conservative policy was felt to be justified. This policy consisted of revision of the labeling of the article, continued dissemination of the facts regarding this hazard to the medical profession by means of general mailings, plus any other practical methods, recall of market packages of the drug so that a revised package circular could be included with specific warnings and reduced dosage recommendations, and continued study of the problem. Newspaper publicity regarding a case of hepatitis and death occurring in San Francisco abetted these efforts markedly.

The results of continued appraisal of this serious problem can be readily summarized:

The number of reported cases of hepatitis associated with iproniazid therapy has reached a figure of 230. Among these 230 cases there were 51 deaths. A cause and effect relationship has been well established and accepted. The estimated incidence and fatality rate is one per 3,000 to 4,000 patients treated with iproniazid, with death occurring in 20 to 25 per cent of the afflicted. The hepatotoxicity is manifested by an insidious onset and a particularly fulminant course, and is not readily differentiated pathologically from infectious hepatitis, other than by severity. Factors that might be used to predict individual susceptibility to iproniazid hepatotoxicity have not been elucidated. Methods of determining impending liver disease have not been found despite the continued caution to employ routine liver-function tests. Once the disease

process has become established the course of the disease is not immediately reversible following discontinuation of the drug. Specific methods to prevent or treat the disease have not been developed. A relationship of dose to incidence does not appear to exist. Reduction of dose was suggested originally because of the known relationship of other severe toxic effects of iproniazid to dose, and as one more positive measure. Review of the individual case histories does not support a thesis that the hepatitis is dose-related; however, there is some evidence that the incidence of hepatitis has decreased somewhat in recent months, which may be interpreted as indicating a dose relationship, since use of the drug in the lower dose ranges has apparently become progressively more popular. It would be very difficult to draw any definite conclusions in respect to relationship of iproniazid hepatotoxicity to duration of therapy. From the available data it does not appear that such a relationship exists. It is true, however, that hepatotoxic effects have occurred only rarely within the first few weeks of therapy. Despite awareness of the serious toxic potentialities of iproniazid those specialists familiar with its use are, for the most part, adamant in their views that iproniazid is a valuable drug and should be kept available for use in treatment of selected patients suffering from mental depression, particularly where other measures have failed and disability is marked. The drug is apparently useful as adjunctive therapy in the treatment of terminal malignancies, in very advanced collagen diseases, and other life-threatening conditions and disability states where aggressive measures are justified and where the psychic stimulant effects of iproniazid appear desirable.

Since the medical experts whom we have consulted consider this drug to be effective in selected patients afflicted with serious disease and since the incidence of this potentially fatal manifestation of drug toxicity does not appear to provoke a therapeutic risk greater than that associated with some other accepted therapeutic measures, we have maintained the opinion that the drug should be kept available for use by physicians. However, we feel that the drug should be employed only by those clinicians who are familiar with treatment with this drug and in patients in whom the risk inherent with this form of therapy is justified by the severity of the illness. We feel that the labeling being distributed with Marsilid at present suitably reflects the cautions necessary to insure proper use of the drug.

EUGENE R. JOLLY, M.D.
Medical Officer, New Drug Branch
U.S. Department of Health, Education, and Welfare

Moreover I would not willingly lay an aspersion of falshood upon any that is desirous of the truth, nor blemish any man by accusing him of an error; but I follow the truth only, and have bestowed both my pains and charges to that purpose, that I might bring forth something which might be both acceptable to good men, agreeable to learned men, and profitable to literature.—WILLIAM HARVEY. *De Motu Cordis,* 1628.

Occlusive Disease of the Carotid Arteries

By ALLEN SILVERSTEIN, M.D.

Within the last 10 years there has been increasing recognition of the frequency of spontaneous occlusions of the carotid arteries as a cause for neurologic deficit, and several reports of successful therapy instituted early in the disease have appeared. Since many patients with symptoms due to carotid occlusion will be seen initially by the general practitioner or internist, increased awareness and knowledge of the condition seem warranted. The clinical and laboratory features of 50 patients with proved carotid occlusions are presented, the varying clinical pictures produced by such occlusions are described, and the potential means of therapy are discussed.

THE recent application of arteriography to the study of cerebrovascular disease has resulted in a revision of several previously held concepts concerning the diagnosis and therapy of the so-called "strokes." One of the most significant of these new concepts has been the acceptance among neurologists of the relative frequency of occlusions of the internal and common carotid arteries as a cause for neurologic deficit. Similarly, the more commonly discussed subjects in the current neurologic literature include many suggested diagnostic and therapeutic means of managing the condition. The purposes of this communication are to analyze the salient features of 50 patients admitted to the Mount Sinai Hospital in whom the diagnosis of carotid occlusion was proved, to restress the frequency and great clinical variability of the disease, and to discuss some therapeutic implications for this common cause of a "stroke."

MATERIALS AND METHODS

The presence of a carotid occlusion was established beyond doubt in all 50 of the patients who form the basis for this report. The occlusion was demonstrated by carotid arteriography in 47 patients and by autopsy in 3. Additional confirmation of the angiographically demonstrable occlusion was available at surgery in 6 patients and at autopsy in 1.

Forty-five of the 47 arteriograms were performed percutaneously, and 2 by cut-down technic. The contrast medium employed routinely since 1956 has been sodium diatrizoate (Hypaque), and all studies have been performed with the aid of serial radiography.* Since 1957 the major portion of the carotid arteries in the neck have been included on the x-ray films of the cerebral angiogram. The criteria for angiographic proof of a carotid occlusion have included visualization of the tip of the Cournand needle on the film.

Thirty of the patients in the present series have been personally observed by me during the last 2 years, and form the basis for a report concerning collateral circulation.[1] The details of all 50 patients have been obtained from the charts of the Mount Sinai Hospital. Where a discrepancy in neurologic findings was recorded during the same period of observation, the findings of the senior observer have generally been accepted. Three of the 50 patients have previously been reported.[2]

RESULTS

Age, Sex, and Incidence. The patients varied in age from 26 to 82 years; 42 were over the age of 50. Thirty-seven of the patients were males, while only 13 were females.

The frequency of recognition of carotid occlusion increased markedly after 1956, almost certainly as a reflection of the increased utilization of arteriography (fig. 1). Two other minor factors may contribute to the more frequent discovery of carotid occlusion as a cause of neurologic deficit: the increased awareness of the condition by pathologists, and thus the more frequent examination of the proximal portions of the internal carotid artery at autopsy; and routine visualization of the neck at the time of cerebral arteriography, and the consequent detection of many partial carotid occlusions.

From the Department of Neurology, Mount Sinai Hospital, New York. U. S. Public Health Service Trainee in Neurology.

*The casette changer and special table utilized for routine angiography have been designed by Dr. Leonard Malis.

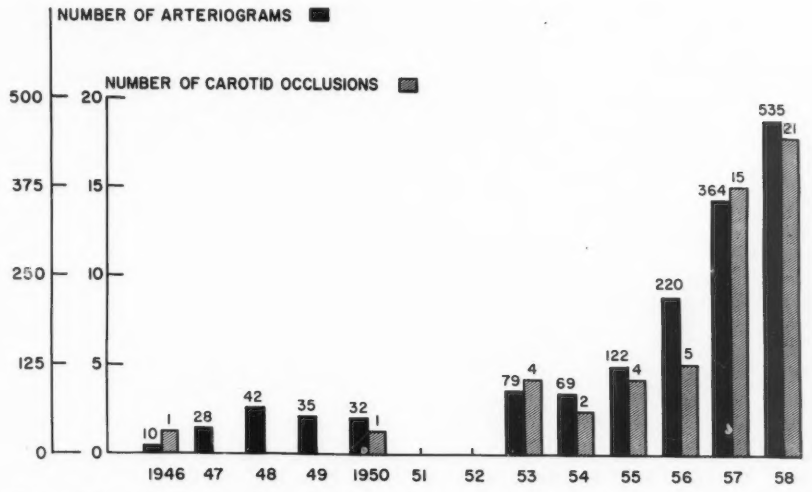

FIG. 1. The number of arteriograms performed and number of carotid occlusions proved each year at the Mount Sinai Hospital. (All arteriograms performed before 1950 were by cut-down technic. There may have been a few other carotid occlusions during this early period.)

Contributing Factors. There was clear evidence of vascular disease elsewhere in 38 of the 50 patients with verified carotid occlusions. Twenty-six patients gave a history of hypertension, or were hypertensive with a resting blood pressure greater than 150/100. A history of angina or electrocardiographic changes indicating myocardial damage were obtained in 24 patients. Sixteen patients gave a history of intermittent claudication in the lower extremities or had diminished to absent peripheral pulses; 3 of them had previous femoral artery occlusions. Severe arteriosclerotic changes were observed in the fundi of 8 patients, and 9 demonstrated significant calcification of the aorta or carotid arteries on routine chest or skull films. Five patients were diabetic, 3 had positive blood serologic tests (probably true positives in all), and the diagnosis of disseminated lupus erythematosus was established in another.

In addition to generalized vascular disease, the history of a few patients suggested other predisposing factors. Thus, one patient had sustained severe head trauma shortly before her symptoms began; a second showed neurologic symptoms 4 days after undergoing general anesthesia for an appendectomy; and a third had undergone neck surgery several years previously. Still another patient—the only one in the present series whose occlusion was thought to be embolic in nature—suffered from chronic empyema and was being treated for septicemia at the time of his occlusion.

Symptoms. The onset of symptoms was quite sudden in 36 patients, 10 of whom rapidly improved, only to develop recurrent episodes prior to admission. In 9 patients the sudden onset was followed by a progressive course.

Fourteen patients had a gradual onset and slow progression of symptoms, as is usually seen with neoplasms. In 3 of these, despite the over-all progression, the symptoms were somewhat intermittent.

The duration of symptoms prior to admission varied from under 1 day in 4 patients to over 2 years in 3. The symptoms included weakness of 1 side of the body or of an upper extremity in 40 patients; unilateral sensory disturbances such as numbness or paresthesias in 18; difficulty with communication in 19; and organic personality changes in 14. In addition, in 14 patients there were seizures,

which were almost always unilateral, involving the paretic arm or face. Ten patients complained of headache, and 4 patients reported dizziness or a depressive reaction. Visual symptoms were described in 9 patients; in 5 of these there was transient diminution or loss of vision in the eye ipsilateral to the carotid occlusion.

Signs. Motor weakness was by far the most common neurologic finding in this series: hemiparesis or hemiplegia was present in 49 of the 50 patients. The deficit was always greater in the upper extremity than the lower, and the face was commonly involved. Reflex abnormalities, such as unilateral hyperactive deep tendon reflexes or extensor plantar responses, were noted in 35 patients; in a few patients the plantar responses were bilaterally extensor. A hemisensory syndrome was detected in 32 patients, and a visual field defect was established in 26. An organic mental syndrome of varying severity was evident in 22 patients, and 21 exhibited some degree of aphasia. Pupillary changes were recorded in 3 patients; in 2 of these the pupil contralateral to the occluded carotid was dilated, while the ipsilateral pupil was dilated in the third. Ataxia, gaze palsy, and extrapyramidal signs were each described in 1 patient. Papilledema was not noted. Optic atrophy on the same side of the occlusion was noted in only 1 patient, and occurred several weeks after his hospitalization.

A statement concerning the equality of the 2 carotid pulses was available in 36 patients; in 11, at least one observer noted unilaterally diminished pulsations; in most cases, however, subsequent examiners could not confirm this finding. An attempt was made to hear a bruit over the carotid arteries, eyeballs, and head in 30 patients, and was successful in only 4. The limited value of auscultation for a bruit or palpation of the carotid pulse has been emphasized previously.[1] Manual compression of the patent carotid artery was recorded in 34 patients, and syncope or seizures were produced by this maneuver in 22 patients. Of the 20 patients in whom ophthalmodynamometry was performed, 16 had significantly diminished retinal artery pressures on the side of their occlusions. The usefulness of these procedures has also been discussed.[1] Distention of the superficial vessels of the face on the side of a carotid occlusion—presumably the effect of collateral circulation—was noted in only 1 patient.

Laboratory Data. Lumbar punctures were performed in 46 patients. In 1 the cerebrospinal fluid was grossly bloody, and had a pressure of 340 mm. water; in 5 other patients the fluid was xanthochromic; in the remaining 40 patients the fluid was clear and under normal pressure. The protein content of the spinal fluid was under 50 mg. per cent in 26 patients, from 50 to 80 mg. per cent in 14 patients, from 80 to 110 mg. per cent in 5 patients, and 111 mg. per cent in 1 patient.

Electroencephalograms were performed in 44 patients. Twenty-nine of these had focal abnormalities (usually slow wave activity) on the side of the occlusion; 6 patients had diffuse abnormalities, and 8 had normal records. In 7 of these last patients, an abnormal record was produced by manual compression of the patent carotid.

X-rays of the skull revealed a significant pineal shift in 2 patients, and films of the neck demonstrated calcification of the carotid arteries in only 2 of the 21 patients in whom such calcification was sought. Pneumoencephalograms were performed in 13 patients; they were normal in 4, showed symmetrically dilated ventricles in 7, and possibly indicated slight displacements in 2 others.

Arteriography. Carotid arteriography was performed in 47 patients. In 23 of these patients the contralateral carotid was also injected, and in 3 vertebral studies were performed. The clinical courses of only 2 patients tended to progress immediately following arteriography. In another 2 patients there were transient neurologic deficits following angiography of the patent carotid; however, these deficits lasted less than 24 hours. No other complications were reported following angiography.

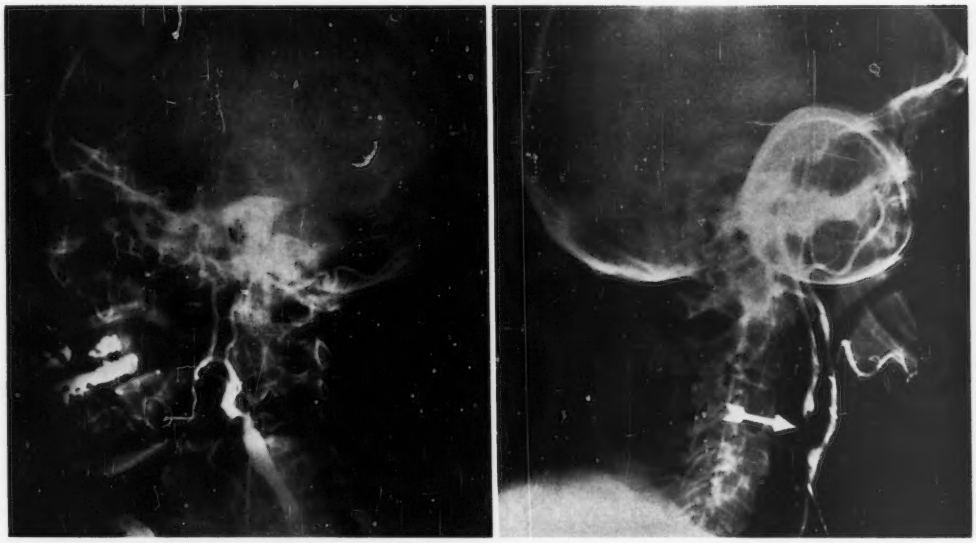

FIG. 2. *Left.* Carotid arteriogram showing complete occlusion of the internal carotid artery at its origin (*arrow*). *Right.* Carotid arteriogram showing partial occlusion at the internal carotid artery at its origin (*arrow*).

Pathology. The brains of the 4 patients with carotid occlusions who came to autopsy revealed more or less extensive softening in the distribution of the middle cerebral artery and a lesser extent in the anterior. Secondary brain stem hemorrhages were present in all 4, and 2 had significant uncal and cingulate herniations. The surgically resected portions of the carotid arteries of the 6 patients who underwent surgery revealed fairly severe atheromatous changes with thrombus formation.

From the arteriographic and autopsy findings, the location and nature of the carotid occlusions were divided as follows: 28 of the occlusions were in the right carotid alone, 20 were in the left alone, and in 2 patients bilateral complete carotid occlusions were demonstrated. Of the 50 patients, 36 had complete occlusions (fig. 2), while 14 had significant partial occlusions (fig. 3). The common carotid artery was the site of occlusion in 2 patients, the carotid "siphon" was occluded in 4 patients, and the distal intracranial portion of the internal carotid was the site of 1 occlusion. The most common site for occlusion, however, was the internal carotid artery in the neck, where such lesions were demonstrated in the remaining 43 patients. These occlusions occurred most commonly at the origin of the internal carotid.

Prognosis and Therapy. Ten of the 50 patients in the present series have died. Death occurred from 48 hours to 2 years after the onset of symptoms, probably due to carotid occlusion. Seventeen patients showed some neurologic improvement and have maintained such improvement. The remaining 23 patients showed no definite change from their condition at the time of admission, or have been lost to follow-up study.

Fourteen patients in the present series have been placed on anticoagulant therapy in an attempt to prevent further vascular occlusion. Six patients underwent neck surgery in an attempt to correct the existing carotid occlusion. The procedures employed were thromboendarterectomy in 4, and carotid-jugular anastomosis in 1 (in 1950). The clot was too extensive for any definitive procedure in the sixth patient. One patient in the present series was treated with intramuscular trypsin.

TABLE 1.—*Frequency of Carotid Occlusions as Determined by Several Means of Study*

	Method of study	Author, reference	Number of patients studied	Percentage with carotid occlusion
I	Routine consecutive autopsies	Hultquist[14]	1300	4.4
		Fisher[10]	432	9.5*
		Samuel[15]	82	6.1
II	Autopsies in patients with cerebrovascular disease	Hutchinson and Yates[16]	83	39.2*
III	Consecutive arteriograms in patients suspected of having intracranial mass lesions	Moniz et al.[6]	500	0.8
		Feiring[17]	500	1.4
		Thomsen[18]	1800	1.2
		Batley[19]	730	1.0
		Norris et al.[20]	349	2.6
IV	Consecutive arteriograms in patients suspected of having cerebrovascular disease	Riishede[21]	100	14.0*
		Tatelman[22]	200	21.5*

*Includes significant stenosis as well as complete occlusions.

Twenty-nine patients received no specific therapy.

Because anticoagulant and surgical therapy have been employed largely only in the last 18 months, the follow-up period is relatively short. At this time, therefore, data cannot be presented concerning the effects of therapy on the natural course of the disease.

DISCUSSION

Historical Background. The first pathologic description of a carotid occlusion dates back to Willis[3] in 1664. An early report of the condition was made by Cushing,[4] in 1900, and Hunt[5] in 1914 described the classical syndrome produced by occlusion of the common carotid artery and stressed the value of palpation of the carotid pulsations in the neck as a means of diagnosis. Interest in carotid occlusion, however, remained slight until the development of cerebral arteriography, and the report of 4 patients so diagnosed by Moniz et al.[6] in 1937. By 1951 Johnson and Walker[7] had collected 101 proved cases of carotid occlusion from the literature and added 6 more. The entity of carotid occlusion was firmly established with the subsequent writings of Fisher,[8–10] Webster and Gurdjian[11–13] and others.

Incidence. Carotid occlusive disease is not rare (table 1). The incidence of carotid narrowing or occlusion in routine, unselected autopsies may be as high as 9.5 per cent,[10] whereas 39 per cent of patients with cerebrovascular disease may have significant carotid stenosis.[16] Carotid occlusion may be diagnosed arteriographically in 14 to 21.5 per cent of patients presenting the acute "stroke" syndrome.[21, 22] Fields et al.[23] found that 25 per cent of patients with cerebrovascular disease have extracranial (i.e., carotid and vertebral) occlusive disease.

Atherosclerosis is by far the most common cause of carotid occlusion. Significant atherosclerosis in the internal carotid artery has been found in 46 per cent of patients over 45,[24] and as many as 80 per cent of older age patients have such atheromas.[15, 25]

Etiology. The various etiologies or predisposing conditions associated with carotid occlusions as reported in the literature are listed alphabetically in table 2. In the present series, moderate to severe degrees of atheroma formation were noted in almost all 10 (6 surgical and 4 autopsy) specimens of the carotid arteries studied. Evidences of atherosclerosis elsewhere in the body, or conditions predisposing to its development, were present in 76 per cent of the 50 patients in the present series.

Clinical Features. The signs and symptoms of carotid occlusion are quite variable, and can mimic those of several other diseases of the brain. Thus, patients presenting progressive neurologic deficit (46 per cent of the present series) may well be suspected of having cerebral neoplasms, especially when headaches (20 per cent) or focal seizures (28 per cent) occur. Although not observed in the present series, papilledema has been reported

to occur with carotid occlusion.[7, 37] Spinal fluid protein may be quite high. If air studies are undertaken as the first definitive diagnostic procedure, the erroneous diagnosis of brain tumor may be further supported by significant displacements of the ventricular system.[41, 42] Such displacements, as well as the 2 shifted pineal bodies noted in the present series, are undoubtedly the results of cerebral edema.

Another common onset of carotid occlusion in a sudden vascular accident (72 per cent in the present series), which may be completely indistinguishable from middle cerebral artery occlusion.[21, 30] The pathologic changes in the brain at autopsy with carotid occlusion are similar to those found with middle cerebral artery occlusion.[32, 37] Thus, hemiparesis, the most constant finding with carotid occlusion (98 per cent in the present series), is characterized by greater severity in the upper than in the lower extremity.

Many patients with carotid occlusions (26 per cent of the present series) have recurrent unilateral manifestations of cerebral dysfunction, the syndrome of "intermittent insufficiency of the carotid arterial system,"[43] or "transient ischemic attacks."[44] Because this syndrome occurs with partial carotid occlusions,[45] it is mistakenly considered to be almost diagnostic of carotid occlusive disease. We have recently seen many patients with intermittent episodes of unilateral cerebral dysfunction and patent carotid arteries at arteriography; in a few of these patients a cerebral neoplasm was eventually demonstrated. An incomplete history or lack of observation during an episode may make differentiation impossible between "ischemic" episodes and postictal phenomena.[44] For these reasons, the increasing use of anticoagulant therapy is not approved in patients with recurrent cerebral episodes—without adequate investigation to determine etiology.

There are other clinical manifestations of carotid occlusions that seem to occur more commonly in the textbooks than in patients. Thus the association of transient monocular blindness with contralateral hemiplegia, although suggestive of carotid occlusion,[9] occurred in only 10 per cent of the present series. The same may be said about the diagnostic significance of an ipsilateral Horner's syndrome[37, 46] (4 per cent), ipsilateral optic atrophy[5] (2 per cent), and dilatation of the superficial vessels of the face[37] (2 per cent). Among the more unusual findings in our series and in the literature are subarachnoid hemorrhage, extrapyramidal signs, depression and impairment of eye movements. It should be noted that completely asymptomatic carotid occlusions may not be rare.[3, 10, 15, 30]

Four reportedly diagnostic bedside tests of carotid occlusion have been frequently discussed in the recent literature. These procedures are (1) palpation of the carotid pulse in the neck and in the pharynx; (2) auscultation of a carotid or intracranial bruit; (3) measurement of the retinal artery pressures (ophthalmodynamometry) and (4) manual compression of the contralateral carotid. In a study[1] of 30 personally observed patients from this series, diminished carotid pulsations were present in only 17 per cent of the pa-

TABLE 2.—*Reported Etiologies and Predisposing Conditions for Carotid Occlusion*

Condition and reference no.	Condition and reference no.
Atlantoid compression[29]	Lupus erythematosus (present series)
Alcoholism[27]	Mucormycosis[34]
Aneurysm with thrombosis[27]	Periarteritis nodosa[27]
Atherosclerosis*	Polycythemia vera[35]
Cardiac surgery[28]	"Pulseless disease"[36]
Cervical rib[20]	Rheumatic fever[37]
Compression by neoplasm[30]	Sinusitis, cavernous[28]
Congenital abnormalities[31]	Syphilis[6, 30]
Embolism[32]	Temporal arteritis[27, 36]
Erythroblastosis[33]	Thromboangiitis obliterans[26, 30, 35, 36]
Infections[27, 30]	Trauma[39, 40]

*Atherosclerosis is considered by almost all authors the major etiologic factor for carotid occlusion.

TABLE 3.—*Incidence of Common Clinical Findings Reported with Carotid Occlusion*

Author and reference no.	No. of patients	Percentage of patients with: Progressive course	Intermittent course	Hemiparesis	Sensory deficit	Aphasia	Field defect	Organic mental syndrome	Headache	es	Ipsilateral Blindness	Ipsilateral Optic atrophy
Johnson and Walker[7]	107*	25	40	80	20	60	11	15	50	20	5	10
Shapiro and Peyton[49]	17	12	59	100	41	53	12	18	6	0	6	12
Thomson[50]	23	48	48	91	70	60	39	9	70	17	4	4
Webster et al.[13]	63	10	27	81	17	36	4	19	21	9	?	6
Boldrey et al.[26]	24	17	33	88	43	17	8	?	83	38	4	?
Jacobsen and Skinhos[51]	27	37	11	70	52	44	22	44	37	4	?	11
Sastrasin[52]	65	63	63	92	31	52	22	37	57	8	3	3
Silverstein	50	46	26	98	64	42	52	44	20	28	10	2

*One hundred and ten of these patients were collected from the literature.

tients. Palpation of pharyngeal pulsations was of no diagnostic aid. A carotid bruit was heard in 13 per cent of the patients. Significant differences of retinal artery pressure were present in 80 per cent, and compression of the patent carotid artery gave "positive" results in 70 per cent of the patients studied. The nature, extent, and rapidity of development of collateral circulation are probably the significant factors responsible for the varied clinical pictures of carotid occlusion.[1]

Angiography. It should be apparent that a definitive diagnosis of carotid occlusion cannot be made on clinical grounds alone. To establish such a diagnosis, and also to exclude space-occupying lesions that may be excised or radiosensitive, carotid arteriography must be performed. The safety of this procedure, even in elderly patients with "vascular disease," is being accepted at increasing numbers of neurologic centers since the development of several newer, less toxic contrast media.

There were only 2 possible persisting complications from the 73 (47 in the occluded carotid, 23 bilateral, and 3 vertebral) angiograms performed in the present series. The recently reported 12 per cent incidence of serious complications in 500 consecutive angiograms at this hospital was derived entirely from experience with older contrast media.[47] Since the completion of this study, 1,000 further angiograms have been performed with the newer, safer contrast media. The incidence of complications in the present series of arteriograms, although the findings are not yet tabulated, is definitely much lower. British workers have reported the incidence of serious complications with Hypaque to be 0.7 per cent.[48] Similar conclusions concerning the newer contrast media, even when employed in patients with cerebrovascular disease, have been reached by many others.[13, 21–23, 26]

Though rare, occasional complications do follow arteriography. In general, in patients with evidence of a focal brain lesion, the amount of information to be obtained by arteriography in most cases outweighs the risks of the procedure. It is recommended, therefore, that every patient with unilateral cerebral disease be evaluated for arteriography after appropriate preliminary study. Only by such means can a presently corrective lesion be excluded, or the diagnosis of a potentially corrective carotid occlusion be established. The evidence that prompt therapy for carotid occlusion, once confirmed, may improve the existing symptomatology or at least prevent further disability will be reviewed subsequently.

Comparison of Present Series with Other Reports. The clinical manifestations of carotid occlusion in this series have not appreciably differed from those previously described (table 3).

Two significant differences between the present series and the majority of other reports deserve comment. In the present series the right carotid artery was found occluded considerably more often than the left. In almost all of the previously published series, left carotid occlusions predominated. No immediate explanation is available for this discrepancy. The sites of carotid occlusion in this series are otherwise similar to those reported elsewhere. As a prelude to a discussion of therapy, it should be stressed that the overwhelming majority of carotid occlusions occur in the neck, a most accessible site.

The second major difference between this and other series of carotid occlusions is the observation here of predominantly symmetrical ventricles in most of the 13 patients in whom pneumoencephalograms were performed. Several previous writers have described unilateral cerebral atrophy on the side of the occlusion.[7, 52] Again the explanation for these conflicting findings is obscure.

Therapy. The results of therapy in the present series have not been presented because the number of patients adequately treated is small, and the follow-up periods are brief. At the present time there are insufficient data to determine which of the 2 major forms of currently recommended therapy for carotid occlusion is to be preferred.

Most writers agree now that previously suggested therapies such as carotid sinus denervation, cervical sympathectomy, carotid-jugular anastomosis, simple resection of a portion of the occluded carotid, and other measures, are probably of little value. The currently accepted forms of therapy for carotid occlusion are anticoagulant therapy and reconstruction of the occluded vessel.

Anticoagulants. Most of the present exponents of anticoagulant therapy for cerebrovascular diseases usually do not perform definitive diagnostic, i.e., arteriographic, studies. Most of these workers would agree that there is little to be gained from such therapy in patients with complete carotid, or other occlusions and maximal neurologic deficit. At least one patient, however, with an angiographically verified complete carotid occlusion had partial patency on repeated angiography following anticoagulant therapy.[53] If the mechanism of action of anticoagulant therapy in cerebral vascular disease is the protection of collateral circulation,[54] then even patients with complete occlusions and maximum deficit should be treated. No adequate data, however, have yet been published to settle this point. In a small series[55] no differences in recovery were detected on the basis of anticoagulant therapy, and 1 patient went on to develop a carotid occlusion (confirmed at autopsy) while on adequate amounts of therapy.

There is evidence, however, that patients with recurrent "ischemic" attacks, as may be seen with partial carotid occlusions, are benefited by anticoagulants.[44, 56-59] It must be stressed that intermittent symptoms are not pathognomonic of carotid or other cerebral occlusions. However, several of the patients in whom intermittent symptoms were relieved by anticoagulant therapy, had findings suggestive of carotid occlusion, i.e., positive ophthalmodynamometric readings that reverted to normal following therapy,[58] unilateral blindness and contralateral paresis,[59] etc. It also seems that patients with progressive neurologic deficit due to carotid and other occlusions are helped by anticoagulant therapy.[44, 58]

The other major area in which anticoagulants appear to be effective is in the reduction of embolic occlusions in the cerebral vessels.[60-63] Carotid occlusions from emboli, as in patients with rheumatic heart disease, have been reported only occasionally,[28, 32] although they may have occurred much more frequently than previously suspected.

The need for strict control of anticoagulant therapy in neurologic patients who may be aphasic or have organic mental syndromes must be particularly stressed. If the once commonly discussed belief[64] is valid, that massive cerebral hemorrhage is precipitated by diseased cerebral vessels and ischemic softening, the hazards of anticoagulant therapy in

patients with occlusive cerebral vascular disease may be great. The most recently reported incidence of cerebral hemorrhage in such patients on anticoagulant therapy was 5 per cent.[63] This hazard may or may not be greater with recent occlusions.

Reconstructive Surgery. Complications may also occur with surgical therapy for carotid occlusion.[65] These may include further cerebral damage from either ischemia or hypotension; the release of emboli during manipulation of the occluded carotid; and the production of postoperative thrombi with extension intracranially or proximally into the aorta.[66] Such complications, however, have been reported rather infrequently with carotid surgery, and probably can be prevented somewhat by utilization of hypothermia during surgery, the avoidance of excessive damage to the vessel wall, and postoperative anticoagulant therapy.[66]

There are 5 currently reported means of reconstruction for carotid occlusion: thrombectomy;[65, 67] thrombo-endarterectomy;[23, 53, 66, 68–72] side-to-side anastomosis between the external and internal carotid arteries;[53, 73] resection of the occluded portion of the carotid and end-to-end anastomosis,[66, 74–76] or replacement with a (venous) graft,[77] or internal-external carotid anastomosis;[65, 70, 78] and bypass grafts made of nylon,[79] Dacron,[23] or a homograft.[80, 81] A temporary polyvinyl shunt has also been employed to facilitate thromboendarterectomy.[69]

Although experience is insufficient at the present time to evaluate these procedures, there is probably little value to be gained from simple thrombectomy or internal-external carotid anastomosis. The relative merits of anticoagulant and surgical therapy for carotid occlusive disease are also unsettled. There is some evidence, however, that patients operated on for partial occlusions or immediately after the onset of a complete occlusion may improve to a greater degree than would occur without therapy. Thus, the recurrent "ischemic" symptoms may completely subside after surgery,[23, 67, 74, 79] postoperative angiograms may show patency for at least several months,[53, 66, 67, 71, 73, 77, 78] and previously abnormal results with ophthalmodynamometry and carotid compression may return to normal.[71, 82]

On the other hand, the majority of patients with complete occlusions of more than several hours' duration, have not tended to show significant improvement from reconstructive procedures. Some of the few patients who have improved following surgery, were subsequently demonstrated to have occluded vessels at postoperative angiography.

To summarize the reported results of anticoagulant and surgical therapy for carotid occlusive disease, (1) both forms of treatment are probably ineffective for long-standing complete occlusions with major neurologic deficit; (2) both therapies may help patients with acute complete occlusions and progressing deficit; (3) both therapies can eliminate the recurrent "ischemic" symptoms frequently seen in patients with partial carotid occlusions; and (4) it is not known at the present time which form of therapy is to be preferred, and under what circumstances each should be employed. The data are also incomplete concerning the complications from either form of therapy.

Conclusions

An attempt has been made to demonstrate how frequently carotid occlusions are responsible for so-called "strokes." The varying clinical pictures produced by such occlusions have been discussed, and the relatively rare occurrence of previously considered diagnostic features was noted. The only 2 such features that occur with significant regularity are positive results with ophthalmodynamometry and carotid compression; even these are not always present and false-positive tests do occur. The procedure of choice for the diagnosis of a carotid occlusion is arteriography. The reasons why the current application of this procedure is considered safe are presented.

There is evidence that both anticoagulant and surgical reconstructive therapy are of

aid in the management of the intermittent or mild symptoms of partial carotid occlusion; they may also help the severe or progressive symptoms associated with a fresh complete occlusion. Unfortunately, these particular patients—those with only a slight hemiparesis, or those asymptomatic in between recurrent "ischemic" attacks—are the very ones upon whom most physicians have been reluctant to perform arteriography.

It is recommended that arteriography be employed in such patients as a definitive diagnostic procedure, because (1) possibly corrective space-occupying lesions can produce such symptoms; (2) anticoagulant and surgical therapy for carotid occlusions may be effective only in such patients; and (3) such patients seem not to be significantly hurt by arteriography with the newer contrast media. This procedure, however, should follow certain basic preliminary studies including a detailed history, complete physical examination, electrocardiogram, and lumbar puncture. The performance of the procedure on an outpatient basis[23] is not recommended.

The institution of potentially hazardous therapeutic measures, such as anticoagulant therapy or neck exploration under anesthesia, prior to the establishment of the diagnosis, is not consistent with the usually accepted principles of proper medical practice. Prompt institution of therapy, once the diagnosis is established, however, may make a significant difference in the recovery of lost function, or in the prevention of further deficit in patients with carotid occlusive disease.

Summary

Occlusions of the carotid arteries may be responsible for over 20 per cent of all acute cerebral vascular lesions. The clinical and laboratory features of 50 proved patients with this disease are presented. The clinical pictures produced by carotid occlusions are quite variable, and can mimic those of brain tumors, middle cerebral artery occlusions, and other conditions. There are few clinically diagnostic features for carotid occlusions. Definitive diagnosis requires arteriographic study. There is some evidence that early institution of anticoagulant or surgical reconstructive therapy in certain patients with carotid occlusions is indicated.

Acknowledgment

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Summario in Interlingua

Il es possibile que occlusiones del arterias carotidic es responsabile pro plus que 20 pro cento de omne acute lesiones cerebro-vascular. Es presentate le characteristicas clinic e laboratorial de 50 patientes confirmate de iste morbo. Le tableaus clinic producite per occlusion carotidic es multo variabile. Illos pote simular tumores cerebral, occlusion de arteria centro-cerebral, e altere conditiones. Il existe pauc aspectos clinico-diagnostic de occlusion carotidic. Le definitive diagnose require studios arteriographic. Certe observationes supporta le these que le precoce institution de therapia anticoagulante o chirurgo-reconstructive es indicate in seligite patientes con occlusion carotidic.

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Medical Eponyms

By Robert W. Buck, M.D.

Bright's Disease. Richard Bright (1789-1858), Lecturer on the Practice of Medicine, and one of the physicians to Guy's Hospital, included in his *Reports of Medical Cases, Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy* (London, Longman, Rees, Orme, Brown, and Green, vol. 1, 1827), the results of his investigations of the pathological conditions associated with albuminous urine. Their epoch-making character has served to attach his name permanently to the whole group of nonsurgical diseases of the kidney. The following quotation is taken from the introductory remarks of the author (page 2):

"The different diseases of the heart and of the lungs on which dropsy depends, and the various changes to which the liver is subject rendering it a cause of impediment to the circulation, are still open to much investigation. . . .

"There are other appearances to which I think too little attention has hitherto been paid. They are those evidences of organic change which occasionally present themselves in the structure of the KIDNEY, and which, whether they are to be considered as the cause of the dropsical effusion or as the consequence of some other disease, cannot be unimportant. Where those conditions of the kidney to which I allude have occurred, I have often found the dropsy connected with the secretion of albuminous urine, more or less coagulable on the application of heat. I have in general found that the liver has not in these cases betrayed any considerable marks of disease, either during life or on examination after death, though occasionally incipient disorganization of a peculiar kind has been traced in that organ. On the other hand, I have found that where the dropsy has depended on organic change in the liver, even in the most aggravated state of such change no diseased structure has generally been discovered in the kidneys, and the urine has not coagulated by heat. I have never yet examined the body of a patient dying with dropsy attended with coagulable urine, in whom some obvious derangement was not discovered in the kidneys."

Iproniazid in Angina Pectoris

A Double-Blind Study

By Milton Shoshkes, M.D., Edwin L. Rothfeld, M.D., Marvin C. Becker, M.D., Aaron Finkelstein, M.D., Calvin C. Smith, M.D., and Fred W. Wachtel, M.D.

There has been considerable recent interest in the treatment of angina pectoris with iproniazid. In this paper the results of a careful double-blind study of its effect are evaluated.

IPRONIAZID (Marsilid),* a hydrazine derivative of isonicotinic acid, originally employed with success as an antituberculosis agent, was later replaced by isoniazid, to avoid central nervous system stimulation as a side effect, first reported by Selikoff, et al.[1] Since then, clinical experience with iproniazid in the field of psychotherapeutics, has shown it to be capable of reversing apathy, asthenia, anorexia, and depression in doses ranging up to 300 mg. per day.[2-4] However, doses of this magnitude have also produced psychoses, both transient and permanent.[5-6]

Investigation into the mode of action of this drug by Zeller and his group established it to be a potent inhibitor in vivo and in vitro of the enzyme monoamine oxidase.[7-9] Shore and his co-workers found this enzyme to be involved in the metabolism of the catecholamines—norepinephrine and serotonin—in both in vivo and in vitro experiments.[10] These catecholamines, moreover, may be of prime importance in the chemical mediation of the brain stem, especially of the centers for autonomic control.[11] Based on these findings, the hypothesis has been advanced that the changes induced in catecholamine metabolism could be responsible for the antidepression action of iproniazid.[12]

Recently Cossio,[13, 14] in Argentina, and Cesarman,[15-17] in Mexico, reported remarkable amelioration of the pain in the angina pectoris syndrome secondary to ischemic heart disease. Their patients had classic symptomatology, namely, pain upon exertion relieved spontaneously by rest and nitroglycerin, though not with uniform success. Moreover, all had abnormal patterns in electrocardiograms at rest and after exercise.

Fifty milligrams of iproniazid were given 3 times daily for 3 weeks, and then the dose was reduced with symptomatic improvement. The results were impressively satisfactory, pain being reduced for as long as 6 months of therapy. Reduction in dosage did not abolish this beneficial effect, but on discontinuance of treatment pains recurred within days and up to 1 month. The course of the illness itself remained unmodified in that the abnormal electrocardiograms remained unchanged. Cesarman[16] followed up his initial study with a larger group of patients, given 150 mg. a day with 100 per cent satisfactory symptomatic relief. Schweitzer and Planta[18] and Master[20, 21] used the 150-mg. dose levels. Patients responded favorably in respect to their anginal pains, in from 2 to 18 days. In Schweitzer's patients, orthostatic hypotension and other side effects at this dosage level forced the halting of medication in 46 per cent. Cossio[19] reported also faintness, weakness, paresthesias, syncope, impotence, and muscular twitching. Furthermore, Zetzel and Kaplan[22] reported on 5 cases of hepatocellular disease accompanying iproniazid medication in doses of 50 to 150 mg. per day.

From the Cardiac Clinic of the Beth Israel Hospital, Newark, N. J.

*Marsilid and placebo tablets were supplied through the courtesy of Hoffmann La-Roche Company Inc., Nutley, N. J.

The experiences of these investigators have emphasized that iproniazid can be "very helpful in angina pectoris, but must be used with caution because of toxic side reactions,"[23] yet was also described as "the first promising drug in a whole professional career of nearly four decades."[24]

We considered that the initial promise of this drug could add a new dimension to the treatment of ischemic heart disease, and therefore, that further delineation of its utility and safety at a daily dose of 50 mg. or less was warranted. In our opinion, such an experiment could be conducted accurately only under the most stringent conditions. Fortunately, there are now available technics of pharmacologic investigation that make possible accurate assessment of a given symptomatic therapy. Of these the double-blind method is the most successful. Katz recommends that in a well-controlled double-blind experiment each patient in the series be subjected also at several different times to both the drug and placebo. This precaution is especially important when the effect on anginal pain is tested.[25]

Methods and Material

Using this recommendation for our model, we set up a double-blind study in our cardiac clinic, where a group of closely observed cardiac patients whose diagnoses of ischemic heart disease with angina pectoris had been confirmed over a long period of treatment. Moreover, they had received most of the well-known therapeutic agents, which could serve as a comparison with the response to any new medication. All had had complete histories and physical examinations. The laboratory studies included a complete blood count, urinalysis, electrocardiogram, chest x-ray, blood glucose, and blood urea nitrogen. Individuals previously treated for angina pectoris were re-interviewed to re-establish the diagnosis. Only patients with anterior chest pain following exertion or emotional upset, which was relieved within 20 minutes by rest, with or without sublingual nitroglycerin, were included in the study. All previous medications and treatment, i.e., sedation, digitalis, nitrites, ataractics, and diuretics including chlorothiazide were continued unchanged.

The patients were seen at 2-week intervals and interviewed according to a question sheet that included presence of angina, the number of attacks of pain and of nitroglycerin tablets used, dyspnea, edema, appetite, strength, well-being, and sleep habits. The responses called for were limited to "better," "unchanged," or "worse," and reports of unpleasant reactions. With each visit, physical examinations were performed consisting of a blood pressure recording, stethoscopic examination of heart and lungs, weight, and inspection for peripheral edema. Laboratory examinations included a serum bilirubin and cephalin flocculation test at each visit to detect any hepatic toxicity, and, when possible, a final electrocardiogram at the conclusion of the study.

The tablets used were identically prepared and bottled. They were labeled "A," "B," "C," and "D." Two of these were placebo and 2 were iproniazid, and the key was withheld from all the investigators until completion of the experiment. The patients were placed on medication in random fashion according to the week in which they were taken into the project. Those seen the first week were given "A," those the second week were begun on "B" and so on for the third and fourth week. The sequence then began over again with "A" for those begun on the fifth week. Patients were followed through in alphabetic sequence with a change in letter each month. Thus, the patient begun with "C," followed up with "D" was then placed on "A" and finally "B." The dose was 1 25-mg. tablet twice daily unless it was reduced for reasons of intolerance. At the conclusion of the experiment, the key was broken and the results were analyzed.

The investigation was then continued, with 25-mg. iproniazid tablets administered daily to 11 patients who remained cooperative. We began the study with 35 patients, but were able to conclude our observations successfully, for purposes of analysis, in a total of 23. They ranged in age from 52 to 85 years; 3 were Negroes, and the remaining were white subjects; 8 were male, and 15 were female. Nineteen received all 4 trials in sequence. Of the remaining 4, 1 received 1 placebo and 1 iproniazid trial; and of the last 3, 2 had 2 iproniazid and 1 placebo trial, while the last had 1 iproniazid and 2 placebo trials. Eight began the trial sequence with "A," 6 with "B," 5 with "C," and 4 with "D."

The greater number of the 12 patients who failed to complete the study were dropped for lack of cooperation and failure to keep appointments as scheduled. Two who refused to permit the serum bilirubin and cephalin flocculation tests were dropped.

Table 1 summarizes the medical and therapeutic background of the patients. All had ischemic heart disease with the anginal syndrome. In 19

there was also hypertensive cardiovascular disease. Eighteen had previous or current cardiac decompensation, and the heart was enlarged at x-ray examination in 16. Two had normal resting electrocardiograms, but 1 demonstrated an unequivocally positive electrocardiogram after an exercise tolerance test. Seven had had previous myocardial infarctions and 2 more had noted previous suspicious, but not completely confirmed episodes. The drugs previously used were continued. Seventeen patients required daily maintenance digitalis, 10 required oral or parenteral diuretics, and 4 were receiving reserpine for hypertensive therapy. All 23 were taking sublingual nitroglycerin tablets in amounts ranging from 2 to 140 tablets per week. Five others took long-acting nitrates, 3 had daily theophylline, and another took meprobamate to ameliorate the painful episodes. In summary, all patients had confirmed ischemic heart disease, due to arteriosclerotic heart disease that was complicated by hypertension in nearly half. All but one had electrocardiographic abnormalities, and most showed evidences of advanced heart disease manifested by cardiac enlargement and congestive heart failure.

Method of Evaluation

To evaluate the results we followed a modified technic of classification, used by Blumgart et al.[26] for analysis of the response to thyroid irradiation by similar patients with angina pectoris. Three categories of results were used:

1. Excellent (marked improvement): patients showing a disappearance of angina or a marked decrease in the frequency and severity of attacks despite an increase in activity. This decrease was estimated as a 75 to 100 per cent reduction in attacks of pain or number of nitroglycerin tablets used per week.

2. Good (worthwhile): patients showing a moderate decrease of their angina or at least the same frequency on an increased activity level. This decrease was measured at approximately a 50 per cent reduction in attacks of pain or number of nitroglycerin tablets used per week.

3. Poor (not worthwhile): includes those with no improvement or worsening, or less than 25 per cent reduction in the number of attacks per week. In this series, we have also included those who had to discontinue the trial medication due to severe side effects.

The fortuitous selection of drugs which presented first the placebo, then 2 months of iproniazid with a final month of placebo, produced 2 consecutive months of active treatment followed abruptly by a replacement by the placebo. With the initial randomization of patients, only those 5 begun with "C," the second iproniazid tablet, did not experience 2 sequential months of the drug. This enabled us to demonstrate pointedly the cumulative pharmacologic effect of the drug.

TABLE 1.—*Summary of Clinical Data*

Age (yrs.)	Sex	Duration angina (mos.)	Number (nitroglycerin wk.)	Hypertension	Cardiac failure	Cardiac enlargement (x-ray)	History myocardial infarction	Electrocardiogram
67	M	180	2-3	Yes	Yes	Yes	No	LVH+S CI
70	F	156	7-24	Yes	Yes	Yes	No	LVH+S CI
73	F	7	14	No	Yes	Yes	No	LVH+S
60	F	216	70-84	No	Yes	Yes	No	LVH+S CI
63	F	18	42-48	Yes	Yes	Yes	No	LVH+S
63	M	12	7-14	No	No	Yes	No	Dig. eff. normal
69	F	84	35	No	No	Yes	No	LVH
69	F	21	14	Yes	Yes	Yes	Yes	LVH PMI
85	M	24	14-21	No	Yes	Yes	No	RBBB CI
77	F	108	14	Yes	Yes	Yes	(?)	PMI
52	M	28	140	No	Yes	No	Yes	PMI
57	M	48	21-28	No	No	No	No	CI
64	M	18	105	No	Yes	No	(?)	CI
58	F	14	14-21	No	Yes	No	No	CI
71	F	48	35	Yes	Yes	Yes	Yes	PMI LVH
49	F	18	42	No	Yes	No	No	LVH+S
66	F	240	28-42	No	Yes	Yes	Yes	LVH+S Dig/CI
70	F	30	14-21	No	Yes	Yes	Yes	LVH+S PMI
62	M	24	21	No	No	No	No	Chr. cor.
61	F	132	2-3	Yes	Yes	Yes	No	LVH CI
67	F	2 wks.	21-28	Yes	No	No	No	CI
65	M	36	21-28	Yes	Yes	Yes	Yes	PMI LVH
69	F	95	7-21	Yes	Yes	Yes	Yes	Normal Resting; Positive Exercise Tolerance

*LVH, left ventricular hypertrophy; S, strain; CI, coronary insufficiency; Dig. Eff, digitalis effect; PMI, previous myocardial infarction; RBBB, right bundle-branch block; Chr. cor, chronic cor pulmonale.

RESULTS

The detailed results of the trials are tabulated in tables 2 to 6.

TABLE 2.—*Effect of Iproniazid upon Angina Pectoris*

	Placebo		Iproniazid		Iproniazid		Placebo	
	No.	%	No.	%	No.	%	No.	%
Excellent	3	15	9	41	14	64	1	5
Good	3	15	5	23	2	9	5	23
Poor	14	70	8	36	6	27	16	72

TABLE 3.—*Effect of Iproniazid upon Blood Pressure*

	Placebo		Iproniazid		Iproniazid		Placebo	
	No.	%	No.	%	No.	%	No.	%
Higher	3	15	3	14	1	5	9	41
Unchanged	13	65	14	63	11	50	10	45
Lower	4	20	5	23	10	45	3	14

TABLE 4.—*Effect of Iproniazid upon Weight*

	Placebo		Iproniazid		Iproniazid		Placebo	
	No.	%	No.	%	No.	%	No.	%
Higher	6	30	5	23	9	41	5	23
Unchanged	10	50	13	59	9	41	5	23
Lower	4	20	4	18	4	18	12	54

Effect on Angina Pectoris (table 2). The first placebo administration gave a total of only 15 per cent excellent and 15 per cent good results. With the use of iproniazid, a marked improvement in response appeared with 41 per cent "excellent" and 23 per cent "good" the first month, and 64 per cent "excellent" with 9 per cent "good" the second month. Our responses were somewhat slower in appearance than those noted by other investigators, taking from 2 to 4 weeks to appear, and were apparently cumulative, judging by the increasing symptomatic benefit with time.

Substitution of the placebo caused a marked and sudden falling off of improvement with only 5 per cent claiming an excellent response and 23 per cent a good response. The total response of "excellent" and "good" of both placebo trials compared well, as did the iproniazid trials. The evidence for cumulation is seen in the increasing number with an excellent response in the second month compared with the first. This in turn was followed by a quick deflation on using the placebo again. This loss of therapeutic effect was also noted within 2 to 4 weeks. A statistical analysis (chi square) between the first placebo and first iproniazid trials gave a p value of 0.09, or probability of 1 in 10 that these results were due to chance. Comparison between the second iproniazid and the second placebo showed a p value of less than 0.001, or a probability of less than 1 in 1,000 that these findings were due to chance.

Effect on the Blood Pressure (table 3). With the first placebo 15 per cent showed increased blood pressure and 20 per cent displayed a lowering. All changes were mild and fluctuating. Similar mild changes were found during the first month on iproniazid, with 14 per cent elevated and 23 per cent depressed. By the second month on the drug, however, 40 per cent showed a blood pressure depression, severe enough in 1 patient to cause postural hypotensive symptoms with mild syncope. This was relieved by discontinuing the drug for 2 weeks, then reinstituting it at a 25 mg. per day level. Only 5 per cent showed an elevation at this time. A quick reversal appeared with switching to the placebo, and a rebound elevation was seen in 41 per cent with only 14 per cent showing a lowered blood pressure, providing evidence for a slow accumulation effect of the drug.

Effect on the Weight (table 4). Weight fluctuations were the least prominent of all observations, with 30 per cent gaining and 20 per cent losing small amounts on the first placebo. On the first iproniazid administration 23 per cent gained and 18 per cent lost weight. By the second month on iproniazid, 41 per cent had gained slightly, while the percentage losing weight remained almost exactly the same, at 18 per cent. The substitution of the final placebo produced a definite change with 54 per cent losing, while 23 per cent gained weight. This again would confirm a cumulative effect of iproniazid, manifested by better appetite and nourishment, with a sudden downward rebound of effect upon switching to the inert material.

Effect on Mood and Feeling of Well-Being (table 5). The first placebo elevated the mood of 45 per cent, while only 15 per cent felt

worse with the tablet. These percentages remained unchanged with the first trial of iproniazid, with 46 per cent feeling better and 18 per cent worse. The second drug trial resulted in the same number (50 per cent) claiming improvement but, only 5 per cent felt worse. Uusing the final placebo tablet, however, reduced the number of those feeling better to 23 per cent, and 13 per cent again felt worse. Thus, the cumulative effect again manifested itself with a general elevation of mood for nearly the entire group under treatment, with only a single subject feeling worse. Discontinuing the active tablet reflected itself in reversal of the induced sense of well-being.

Effect on Untoward Reactions (table 6). Placebos, though pharmacologically inert, have been demonstrated to produce a wide variety of toxic reactions, and in general can worsen the symptoms of up to 20 per cent of an experimental population.[27] Similarly, during the first placebo attempt, 1 mild and 1 severe reaction in 10 per cent of the group were produced. The first use of iproniazid, however, produced a definite increase in incidence of reaction to 23 per cent mild and 4 per cent severe. Repeated nausea and vomiting forced us to discontinue the drug "B," but the subject successfully took "C" in the same dose level. "B" and "C" were both iproniazid. By the second month, 36 per cent experienced mild and 14 per cent severe side reactions. One patient with a postural hypotensive reaction, required halving of the dose. However, this total of 50 per cent of reactions included for the most part, mild and relatively unimportant symptoms, but, the increasing number of reactions, again demonstrates a cumulation of pharmacologic effect of the drug. Return to the placebo brought 6 per cent mild and 5 per cent severe reactions.

The increasing number of reactions with prolonged use of the drug emphasized the need to determine its effectiveness at the lower dose level of 25 mg. per day. Eleven patients were placed on this amount and followed for at least 1 month further. Nine of them reacted as favorably as with the higher dosage. In 2, a return to the 50-mg. level was necessary. Two patients (19 per cent) experienced mild untoward reactions on this dose. The laboratory studies showed no abnormalities of liver function with the serial determinations of serum bilirubin and cephalin flocculation. No signs of hepatotoxicity were detected in any subject. One month after discontinuing the study, 1 patient was admitted to the hospital for the treatment of painless icterus. The gallbladder was not visualized after both oral and intravenous cholangiography, cholelithiasis with cholecystitis was therefore seriously considered as the etiologic background. Her course was benign and she was discharged in 4 weeks in an asymptomatic condition.

TABLE 5.—*Effect of Iproniazid on Mood and Feeling of Well-Being*

	Placebo		Iproniazid		Iproniazid		Placebo	
	No.	%	No.	%	No.	%	No.	%
Improved	9	45	10	46	11	50	5	23
Unchanged	8	40	8	36	10	45	14	64
Worsened	3	15	4	18	1	5	3	13

TABLE 6.—*Untoward Reactions of Placebo and Iproniazid*

	Placebo		Iproniazid		Iproniazid		Placebo	
	No.	%	No.	%	No.	%	No.	%
Mild	1	5	5	23	8	36	3	14
Severe	1	5	1	4	3	14	1	5
Total	2	10	6	27	11	50	4	19

The repeat electrocardiograms were likewise without significant change. Of the 17, 12 remained unchanged, 4 improved slightly, and 1 became worse. No patient experienced an acute myocardial infarction during this observation. One subject demonstrated transient signs and symptoms of a minor cerebrovascular accident, probably a small cerebral artery thrombosis. She remained ambulant and participated through the study with rapid and complete resolution of her episode within 2 weeks.

DISCUSSION

Beecher[28] has specified the requirements for appraising drugs, the efficacy of which is tested by the patients subjective responses. These conditions include (1) cooperative in-

dividuals who report on response, (2) the use of a double unknown (placebo-double blind), (3) randomization of order, (4) correlation of data, and finally, (5) mathematical evaluation. Our study fulfills all these criteria, including also the stringent condition proposed by Katz,[25] i.e., presentation of the unknowns, on 2 separate occasions. Most important in a small group is the statistical correlation, which was highly significant in this study. Thus, investigation of 10 times the number under the same conditions should not change our finding of a positive symptomatic benefit with the use of iproniazid.

We consider that this study provides a new opportunity for reevaluation of the drug at the recommended dose level of no more than 50 mg. per day. The percentage of relief of symptoms was as high in this study as in those previously reported with 150 mg. doses. Moreover, we were successful even with doses of 25 mg, and a likely further reduction is indicated once symptomatic improvement is attained. The demonstration of a gradual accumulation of pharmacologic effect over the 2-month period emphasizes the need for patience in awaiting the desired response. The drug should be reduced at stepwise intervals of 1 or 2 weeks until the lowest effective dose is reached. Thus, the quandary so aptly described by Master[20] may be solved.

This worker using the recommeded dosage of 150 mg. per day in 74 patients found that "In my long experience with innumerable drugs for coronary heart disease, none has approached the subjective relief attained by iproniazid." However, because of the high number and serious nature of untoward side effects, he was forced to discontinue the use of iproniazid, pending the development of a similar but less toxic compound. It is our opinion, that except for a possible specific hepatotoxicity, other reported side effects are manifestations of overdosage. We did not find that such untoward side effects were necessary correlation to a positive drug response; for example, while postural hypotension diminished on reduction of the drug, the symptomatic relief of anginal pain persisted.

The mechanism of action of this drug is beyond the limits of our investigation. Speculation as to its mode of action points to some change in the catecholamine metabolism within either the myocardium or myocardial blood supply. Raab,[29] in a recent review of the chemical control of the metabolism and function of the heart, pointed out that the neurohormones, norepinephrine and acetylcholine, are liberated and react locally within the heart. Moreover, circulating epinephrine and norepinephrine are avidly absorbed by the myocardium. Insofar as the oxygen consumed during the cardiac recovery phase is augmented by the catecholamines and reduced by acetylcholine, these neurohormones regulate the energy metabolism of the heart. The exact pharmacology of catecholamines in myocardial metabolism and function is still being evolved. Lochner et al.[30] found that the oxygen saturation of the coronary sinus rose in the intact dog after the intravenous infusion of epinephrine, norepinephrine, and acetylcholine. Feinberg and Katz,[31] using a different technic, found that infusion of catecholamines also diminished the coronary arteriovenous oxygen difference, while increasing the coronary blood flow and the available oxygen to the myocardium. Infusions of iproniazid in the isolated mammalian heart increased the coronary blood flow.[32] moreover, Pletscher and Pellmont also found a long-lasting rise in the catecholamine content of the heart of guinea pigs.[33] These observations point to a plausible sequence of events in which long-term administration of a potent monoamine oxidase inhibitor initially increases the catecholamine content of the myocardium. These neurohormones can dilate the coronary vessels, increasing the oxygen supply to the myocardium while enhancing its metabolic utilization of the available oxygen. This pharmacologic action has a favorable effect on angina pectoris secondary to ischemic heart disease.

In addition to the pharmacologic effects upon anginal pain the more favorable emotional outlook experienced by patients while on iproniazid for 2 months contrasted with the

marked let-down sensed on sudden switching to a placebo must not be overlooked. Others[34–36] have emphasized the strong effect of emotions on the course and prognosis of angina pectoris. There seems little doubt that such a more optimistic outlook exhibited by our patients was a potent factor in their achieving symptomatic relief from pain.

Summary

An evaluation of iproniazid in the syndrome of angina pectoris in ischemic heart disease is presented. A "double blind" experiment was performed with 4 unknowns, 2 of which were iproniazid and 2 placebo given separately at monthly intervals. The use of iproniazid was judged effective in relieving the pains of a total of 64 per cent and 73 per cent of the group on 2 separate periods, while the placebos were effective in only 30 per cent on 2 separate periods. These differences, analyzed statistically, were shown to be significant. The effects of this drug were slowly cumulative as evidenced by an increasing rate with time of both therapeutic effectiveness and of untoward reactions. Iproniazid at the dosage level employed also produced a mild hypotensive effect and an elevation of mood, and aided in maintaining body weight. There was no change in the clinical course or in the progression of the primary heart disease.

The initial dose level of 50 mg. per day was reduced satisfactorily to 25 mg. per day in 9 of 11 subjects. Doses over 50 mg. per day should be used only initially and not in ambulatory patients. When a therapeutic response is achieved, the maintenance dose of iproniazid should be continually reduced in stepwise fashion at 1- or 2-week intervals until the minimum effective dose is found for the individual patient.

Summario in Interlingua

Es presentate un evaluation de iproniazido in le therapia del syndrome de angina de pectore in morbo de corde ischemic. Esseva executate un experimento "bis-occulte" con quatro medicationes incognoscite: 2 de iproniazido e 2 de un preparato fictitie. Illos esseva administrate separatemente a intervallos mensual. Le uso de iproniazido esseva considerate como resultante in un alleviamento del dolores in un total de 64 e 73 pro cento del casos studiate in 2 differente periodos experimental. Le uso del preparatos fictitie produceva un alleviamento del dolores in solmente 30 pro cento del casos in 2 periodos. Le analyse statistic monstrava que iste differentias esseva significative. Le effectos del droga esseva lentemente cumulative. Isto esseva apparente per le progressive efficacia therapeutic e le progressive augmento del reactiones adverse. Iproniazido in le dosage usate produceva etiam un leve effecto hypotensive. Illo elevava le spiritos del patientes e esseva de adjuta in mantener lor pesos corporee. Esseva notate nulle alteration del curso clinic o del progresso del morbo cardiac primari.

Le dosage diurne de initialmente 50 mg esseva reducite satisfactorimente a 25 mg in 9 ex 11 subjectos. Doses de plus que 50 mg deberea esser usate solmente al initio e non del toto in patientes ambulatori. Quando un responsa therapeutic es obtenite, le dose de mantenentia de iproniazido deberea esser reducite continuemente a intervallos de 1 o 2 septimanas usque le efficace minimo es determinate pro le patiente individual.

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Familial Patterns in Hypertension and Coronary Heart Disease

By CAROLINE BEDELL THOMAS, M.D.

The family histories of Johns Hopkins medical students were studied in detail and independent evaluations were made of the prevalences of hypertension and of coronary heart disease among the students' parents and grandparents. The hereditary factors in hypertension and coronary heart disease were studied and some interesting patterns of differences in sex inheritance became apparent that need further investigation.

THE investigation of genetic factors in hypertension is complicated by the pleomorphic nature of the disorder. Although elevation of arterial pressure is the fundamental attribute of all forms of hypertension, uncertainty exists as to the interrelationship of the various clinical types. For example, essential hypertension and the hypertension secondary to pyelonephritis or toxemia of pregnancy may be etiologically independent. On the other hand, it is possible that such secondary hypertension occurs chiefly in persons who are highly susceptible to hypertension in the first place. Another confusing fact is that disability and death in clinical hypertension due to strokes, heart attacks, and renal failure are more closely linked to atherosclerosis than to elevation of arterial pressure per se.

Accordingly, as a step toward understanding how to predict and ultimately to prevent such cardiovascular catastrophes, we embarked in 1946 on a long-term investigation of the precursors of hypertension and coronary heart disease, using the Johns Hopkins medical students as subjects. The study was based on the hypothesis that the origins of these 2 serious diseases are multifactorial and closely intertwined, so that factors common to both may often be present in the same individual. Not only have we studied the students' physiologic, metabolic, and psychological characteristics, but their family histories as well, to determine the nature of each student's inheritance. By following these subjects over the years, it is our purpose to determine which factors are related to the early onset of hypertension or coronary disease.

Successive classes of medical students have cooperated in collecting data regarding the occurrence of all types of hypertension and coronary disease among their own parents, aunts, uncles, and grandparents. Our method has been previously described in detail.[1] When all the available facts for each relative were assembled, a final rating of "present," "absent," "questionable," or "unknown" was made for hypertension and for coronary disease independently. Our rating for hypertension was based on clinical diagnosis by physicians, rather than on a single blood pressure measurement, the criterion used by Pickering and his co-workers.[2] This was necessary, because the majority of the grandparents in our series were no longer living. The parents' generation was in the mid fifties on the average. Approximately 11 per cent of the fathers and 14 per cent of the mothers were reported to have hypertension, while 9 per cent of the fathers and 2 per cent of the mothers had coronary disease.

From the Johns Hopkins School of Medicine, Baltimore, Md.

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TABLE 1.—*Parental Hypertension and Coronary Disease among 724 Johns Hopkins Medical Students*

Students reporting	No.	%
A parent's death from these causes (including sudden death)	57	7.9
A parent with severe disease (stroke, coronary occlusion, heart failure)	51	7.0
A parent with moderate disease (angina pectoris, enlarged heart, etc.)	26	3.6
A parent with mild hypertension	56	7.7
Total with positive parental history	190	26.2

The spectrum of cardiovascular disease among the parents of Johns Hopkins students is shown in table 1.[3] In addition to the categories shown there, approximately 10 per cent of the subjects had a parent with questionable hypertension or coronary disease. Thus, less than two thirds of the students can say that both parents are definitely free from these disorders.

We have previously reported the prevalence of hypertension and coronary disease in 2 successive generations.[1] Figure 1 gives a comparison of the prevalence of these disorders among the offspring of 3 types of mating: Type I, where both marital partners were affected, type II, where 1 partner was affected, and type III, where neither partner was affected. The proportion of affected offspring was greatest where both parents suffered from some form of these disorders, and least where neither parent was affected. According to whether both, one, or neither of the parents was affected, the prevalence in the offspring was 22.2 per cent, 12.3 per cent, and 8.1 per cent respectively. Thus, 2.7 times as many offspring of a type I mating had some form of hypertension or coronary disease as did the offspring of a type III mating, while the rate for type II was intermediate. This descending gradation in prevalence for the 3 types of mating was statistically highly significant.

What if the 3 types of mating are based on one disorder, disregarding the presence or absence of the other? Where matings are based on hypertension, there is a highly significant gradation in the prevalence of hypertension among the offspring (fig. 2). The prevalence of coronary disease among the offspring of 3 types of mating based on hypertension shows a similar gradation which is not significant. When matings are based on coronary disease, a highly significant gradation in the prevalence of coronary disease among the offspring is found. Again, there is a similar gradation in the number of offspring showing the other disorder—this time, hypertension. Accordingly, whichever disorder we start with, the patterns of gradation of the 2 disorders in the offspring are similar in direction, and the prevalences of some form of the disorders in the offspring show highly significant differences among the 3 types of mating. All of these findings taken together, suggest a genetic interrelationship between hypertension and coronary disease. Our sibling data also point in that direction, but are as yet statistically inconclusive.

Another aspect of our family studies has excited our attention: there appear to be sex differences in the transmission of these 2 disorders. Where the 3 types of mating based on hypertension are considered, the gradation in prevalence among the offspring came chiefly from the female offspring (fig. 3).[4] Where both parents were hypertensive, the occurrence among the female offspring was 20.7 per cent; where one parent was hypertensive, 13.0 per cent, and where neither parent was hypertensive, 4.5 per cent. The incidences among the male offspring were much more alike: 11.1, 10.0, and 7.9 per cent. Conversely, where the presence or absence of coronary disease is the basis for the 3 types of matings, the gradation in prevalence stemmed chiefly from the male offspring, who showed a 21.2, 8.2, and 4.1 per cent incidence respectively where both, one, or neither of the parents was affected (fig. 4). Percentage prevalences for the female offspring were much lower and showed little difference: 4.1, 2.4, and 2.6 per cent respectively. Presumably, the difference between men and women in age of onset of coronary disease is a complicating factor in this comparison.

Pursuing the apparent sex differences in regard to hypertension further, we divided the students' parents into 4 groups according to sex and the presence or absence of hypertension. Where mothers were hypertensive, their mothers (the grandmothers) had more than twice as much hypertension as their fathers (the grandfathers), namely, 41.7 versus 19.4 per cent (fig. 5). They also had twice as much maternal hypertension as did unaffected mothers (41.7 versus 19.5 per cent), while there was no difference in the prevalence of paternal hypertension (19.4 versus 19.0 per cent). A similar comparison was found in the occurrence of hypertension in fathers of affected and unaffected fathers—28.6 versus 15.0 per cent, nearly a twofold difference. We have also compared the incidence of hypertension in male and female siblings of hypertensive mothers and fathers (fig. 6). Where the probands were women, their female siblings had twice as much hypertension as their male siblings, whereas where the probands were men, their male siblings had nearly twice as much hypertension as their female siblings.[1]

Since the publication of our findings, somewhat similar observations have been made by Allen and Spuhler.[5] In their recent studies of systolic pressure levels among Navaho Indians, they found good correlation between systolic pressures when sisters were compared with sisters and brothers with brothers, but almost none when they compared siblings without regard to sex. In 2-generation comparisons, the father-son and mother-daughter correlations were the highest. They concluded that there is a "sex specific" tendency in the inheritance of blood pressure. These trends agree closely with our findings.

In summary, our studies indicate that both hypertension and coronary disease show a gradation in the prevalence of each disorder in the offspring of 3 types of mating. This gradation is consistent with the Mendelian law of segregation, in that the greatest proportion of affected persons was always found among the offspring of 2 affected parents and the smallest proportion among the offspring of two unaffected parents. The gradation was most marked where the presence or absence of the same disorder was studied in 2 successive generations. However, a less striking gradation in the same direction was noted where

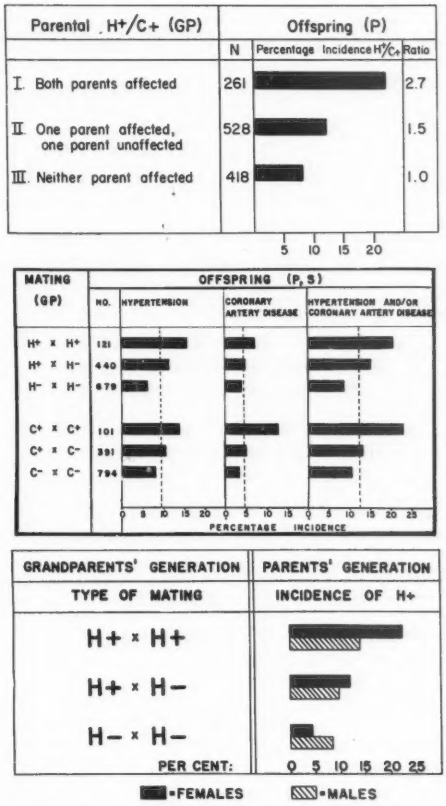
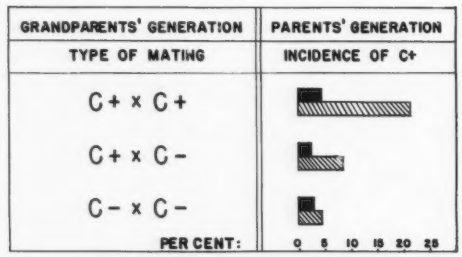
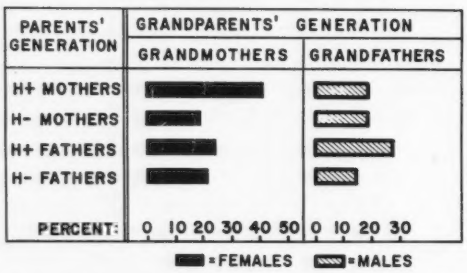


FIG. 1 *Top.* Comparative incidence of hypertension and coronary heart disease (H+/C+) among the offspring of 3 types of mating. *GP*, grandparents of the medical students; *P*, parents, aunts and uncles of the medical students. (From Thomas, C .B.: Ann. Int. Med. 47: 389, 1957.)

FIG. 2 *Middle.* Comparative incidence of disorders among the offspring of 3 types of mating based on (1) hypertension and (2) coronary disease. *GP* as in figure 1. *P*, *S* in figure 2 is the same as *P* in figure 1; both indicate the parents and their siblings, i.e., the aunts and uncles of the medical students. *(Adapted from figure 8, Thomas, C. B., and Cohen, B. H.: Ann. Int. Med. 42:90, 1955.)*

FIG. 3 *Bottom.* Sex differences in the inheritance of hypertension (H+). *(From Thomas, C. B., Am. J. M. Sc. 224: 367, 1952.)*





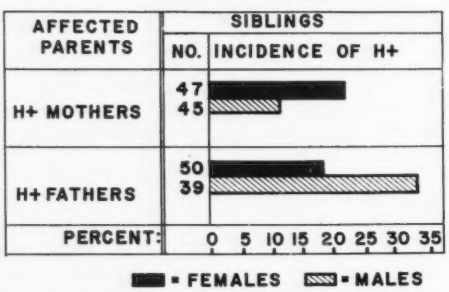


FIG. 4 *Top.* Sex differences in the inheritance of coronary disease (C+).

FIG. 5 *Middle.* Sex differences in the inheritanc of hypertension (H+). Percentage incidence of hypertension among grandmothers and grandfathers according to the presence or absence of hypertension in the parents' generation and the sex of the parent.

FIG. 6 *Bottom.* Sex differences in the inheritance of hypertension (H+). Percentage incidence of hypertension among the female and male siblings of hypertensive mothers and fathers.

hypertension was considered in one generation and coronary disease in the other, in either of the 2 possible sequences. Certain sex differences in the familial appearance of hypertension and coronary disease were noted. In regard to hypertension, the mothers and sisters of hypertensive women had more than twice as much hypertension as their fathers and brothers. On the other hand, the fathers and brothers of hypertensive men had almost twice as much hypertension as their mothers and sisters.

These findings are presented as areas for further exploration. Most of the studies discussed were based on material from our first 5 classes only. Conclusions derived from such a limited series will doubtless require some modification, but the trends seem unmistakable. As our numbers grow, the familial patterns will gradually emerge with sharper definition and increasing variety.

Summary

Studies have been made of the prevalence of hypertension and of coronary heart disease in 2 successive generations of subjects.

The greatest proportion of affected persons was always found among the offspring of 2 affected parents and the smallest proportion among the offspring of 2 unaffected parents. This finding is consistent with the hypothesis that hypertension and coronary heart disease are hereditary disorders, at least in part.

While the most striking correlations were seen when the prevalence of the same disorder was studied in 2 successive generations, similar but less striking correlations were found when hypertension was investigated in one generation and coronary disease in the other.

The female relatives of hypertensive women were found to have more than twice as much hypertension as their male relatives, while the male relatives of hypertensive men had almost twice as much hypertension as their female relatives.

Summario in Interlingua

Esseva studiate le prevalentia de hypertension e de morbo cardiac coronari in 2 successive generationes de subjectos.

Le plus alte proportion de subjectos afficite esseva semper trovate inter le prole de 2 afficite parentes. Le plus basse proportion de subjectos afficite esseva semper trovate inter le prole de 2 non-afficite parentes. Iste constatation concorda con le hypothese que hypertension e

norbo cardiac coronari es disordines heredi-
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Le plus frappante correlationes esseva con-
tatate quando le prevalentia del mesme dis-
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Le consanguineos feminin de feminas hy-
pertensive monstrava un incidentia de hyper-
tension plus que duo vices illo de lor consan-
guineos mascule. Le consanguineos mascule
de masculos hypertensive monstrava un inci-
dentia de hypertension plus que duo vices illo
de lor consanguineos feminin.

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There is strong circumstantial evidence to show that blood cholesterol levels are causally associated with atherosclerosis and that these levels may be partly controlled by diet. Neither of these propositions has been proved but enough is known to suggest the value of wider testing to determine their validity. In this study the use of vegetable oils made it possible to provide much the same kinds of food to which people were accustomed and the pattern developed makes use of ordinary foodstuff, is easily prepared, and is widely acceptable. This diet reduces serum cholesterol levels in normal people and in many hypercholesteremic people and may be more effective than a simple low-fat diet. The key lies in the use of a modified unsaturated vegetable oil in combination with low saturated fat foods. The principal source of fat was a mixture of 94 per cent cottonseed, 1.5 per cent monostearin, 1.5 per cent distearin, and 3 per cent tristearin. It was tested first over a 21-day period in 4 active young physicians and later by study continued for 6 to 24 months in 16 patients with atherosclerosis. The results suggest its use in a broader test relating blood cholesterol levels with atherogenesis. It is pointed out that there is much to be learned before we can recommend such a pattern as a proper modification of the American bill of fare which chance and choice and custom have approved.

KITCHELL

Pitfalls in the Electrocardiographic Diagnosis of Left Ventricular Hypertrophy

A Correlative Study of 200 Autopsied Patients

By ARTHUR H. GRIEP, M.D.

The electrocardiographic diagnosis of left ventricular hypertrophy is uncertain at best and is largely based on useful clues. Reliance on the presence or absence of abnormally high QRS voltage or any of the other presently accepted criteria may lead to error. The author undertook evaluation of the reliability of the various electrocardiographic criteria of left ventricular hypertrophy in a study correlating electrocardiographic and postmortem findings.

CRITERIA in current use for the electrocardiographic diagnosis of left ventricular hypertrophy are lacking in both reliability and specificity. Many observers now use abnormally high QRS voltage as an index of hypertrophy. For example, Sokolow and Lyon[1] concluded that hypertrophy of the left ventricle was present when the sum of RV_5 or RV_6 and SV_1 exceeded 35 mv. However, the fact that many patients with left ventricular hypertrophy fail to show abnormal QRS voltage greatly diminishes the usefulness of such measurements. Other electrocardiographic findings suggestive of left ventricular hypertrophy are unquestionably helpful. These include the sloping S-T segments and the minus-plus T waves in left ventricular leads and, in some instances, a delayed onset of the intrinsicoid deflection in the same positions. The material which follows is an attempt further to evaluate the reliability of these criteria.

When fulfilled, the criteria of Sokolow and others[1, 2] constitute, apparently, an extremely reliable diagnostic sign of left ventricular hypertrophy. This has further been confirmed by Scott[2] and other investigators. However, the data to be presented show that the voltage criteria of left ventricular hypertrophy are more often absent than present even when hypertrophy is severe. Since it is the belief of many that left ventricular hypertrophy is unlikely or impossible unless the criteria of abnormal QRS voltage are met, it seems timely to reassess the problem of the electrocardiographic diagnosis in left ventricular hypertrophy.

This evaluation was made by a study of antemortem electrocardiograms in a large number of patients who exhibited unmistakable left ventricular hypertrophy at autopsy. Correlation in these patients was attempted for all electrocardiographic criteria including voltage requirements. Additionally, factors were considered which modify voltage on the body surface.

MATERIAL AND METHODS

The material for this report was derived from an analysis of 200 consecutive patients in whom the Department of Pathology of the Massachusetts General Hospital found unequivocal left ventricular hypertrophy at autopsy, and in whom 1 or more conventional 12-lead electrocardiograms had been taken within 3 weeks prior to death. Patients under the age of 25 years were excluded to eliminate electrocardiograms in which high QRS voltage might be considered normal. All patients (by chance) were Caucasians and showed the expected spread as regards age, sex, and so forth. In nearly the entire group of patients cardiovascular disease was the underlying cause of death. Significant anatomic left ventricular hypertrophy was considered to exist when the postmortem heart weight exceeded 0.5 per cent of the patient's total body weight. As an added check left ventricular hypertrophy was confirmed by correlating the heart weight with the body length according to the tables of Zeek.[4] All cases were discarded from the series in which the postmortem finding

From the Departments of Medicine and Pathology, Massachusetts General Hospital, Boston, Mass.

of left ventricular hypertrophy was in any way equivocal, or in which there was evidence or reason for significant combined ventricular hypertrophy.

After 200 consecutive autopsied patients were collected who stringently met all of the above criteria, the antemortem electrocardiograms of each patient was analyzed in detail. This study included careful measurements of QRS voltage and use of the criteria of Sokolow.[1] Other electrocardiographic abnormalities of left ventricular hypertrophy were tabulated, and finally each electrocardiographic deviation other than left ventricular hypertrophy was recorded. In an effort to make this study as "blind" and unbiased as possible, all electrocardiograms were read without knowledge of the pathologic diagnoses.

Results and Comments

The various electrocardiographic findings in the entire series of 200 patients with autopsy-proved left ventricular hypertrophy are listed in table 1.

Normal Electrocardiogram. Twenty-three patients exhibited electrocardiograms that were normal in all respects.

Abnormally High QRS Voltage. Forty-four patients (22 per cent) satisfied the Sokolow criteria. They were present as the sole manifestation of left ventricular hypertrophy in only 3 cases (1.5 per cent). If those patients are excluded in whom there were electrocardiographic findings of frank myocardial infarction or bundle-branch block, these values increase to 32 per cent and 2 per cent respectively.

ST-T Changes of the Left Ventricular Hypertrophy Type. These changes consisted of the classical sloping of the S-T segments with minus-plus T waves in the left ventricular leads. There were 96 patients in this group of which 41 had abnormal QRS voltage. Fifty-five cases had unremarkable voltage and showed no other electrocardiographic abnormalities except for isolated instances of small anteroseptal or posteroinferior myocardial infarctions which did not alter the ST-T changes.

These ST-T abnormalities are thought by many to be the most reliable indication of left ventricular hypertrophy. They probably are the manifestations of strain or dilatation of the left ventricle which serves also as a stimulus to hypertrophy. It seems logical that these changes should precede and accompany abnormal QRS voltage, which is assumed to be a reflection of the increased muscle mass of the hypertrophied ventricle.

Classical Myocardial Infarction. This group included classical myocardial infarctions in differing degrees of chronicity and in various locations. Since it was clearly evident that most myocardial infarctions obviated abnormally high QRS voltage, no attempt was made to set forth a purposeless classification of the myocardial infarctions present. Localized anteroseptal or posteroinferior myocardial infarctions that did not influence the abnormal QRS voltage criteria or the classical ST-T

Table 1.—*Electrocardiographic Findings in 200 Patients with Left Ventricular Hypertrophy Proved at Autopsy*

Electrocardiographic findings	Number	Percent
A. Abnormal QRS voltage criteria *fulfilled* (44 patients, 22%)		
1. As sole manifestation of left ventricular hypertrophy	3	1.5
2. Together with ST-T changes of left ventricular hypertrophy type	41	20.5
B. Abnormal QRS voltage *absent* (156 patients, 78%)		
1. Normal electrocardiogram	23	11.5
*2. ST-T changes of left ventricular hypertrophy type	55	27.5
3. Classical myocardial infarction	31	15.5
4. Myocardial infarction with peri-infarction block	16	8
5. Isolated left bundle-branch block	7	3.5
6. Isolated right bundle-branch block	9	4.5
†7. Patients in whom some tracings showed QRS voltage abnormalities and others did not	10	5
8. Nonspecific T-wave abnormalities	5	2.5
Total	200	100

*Some of these showed evidence of anteroseptal myocardial infarction or postero-inferior myocardial infarction.

†This group is included in the category of "abnormal QRS voltage absent" because the electrocardiograms did not satisfy the Sokolow criteria in every serial tracing.

changes of left ventricular hypertrophy are not included in this group (vide supra).

Myocardial Infarction with Peri-infarction Block. In all of these instances except 1 the Sokolow criteria were not met. Presumably this finding can be attributed to the large mass of infarcted myocardium together with the associated vector shifts that characterize myocardial infarctions in this category.

Isolated Left Bundle-Branch Block. As Sokolow has pointed out, abnormal QRS voltage criteria are not applicable in the presence of left bundle-branch block. It does seem likely, however, that total QRS area rather than voltage may be abnormal in this situation.

Isolated Right Bundle-Branch Block. All electrocardiograms showing right bundle-branch block failed to meet abnormal QRS voltage criteria. The main reason was the lack of the usual deep S wave in V_1. Similarly, the extra tall T waves in the outer precordial leads due to right bundle-branch block, interfere with the ST-T abnormalities which might otherwise result from left ventricular hypertrophy.

Serial Tracings in which Some Showed QRS Voltage Abnormalities and Others Did Not. In a few patients in whom several electrocardiograms were taken during the 3-week antemortem period, some records met the Sokolow criteria, and others did not. Except for the QRS voltage differences, these serial tracings were otherwise entirely similar. On the basis of voltage criteria alone, it would appear that a patient could have left ventricular hypertrophy one day and not the next. There was no evidence that these differences were technical.

Nonspecific T-wave Abnormalities. This small group of 6 patients did not satisfy the Sokolow criteria or show any electrocardiographic abnormality suggesting left ventricular hypertrophy, and yet some of the largest left ventricles were found in this group. Pathologic diagnoses included primary amyloid disease, hemochromatosis, para-amyloid disease, endocardial fibroelastosis, idiopathic interstitial myocarditis, and interstitial myocarditis associated with acute glomerulotubular nephritis.

RV_6 Greater Than RV_5. When this study was undertaken it was suggested[5] that an RV_6 of greater voltage than RV_5 might indicate the presence of gross left ventricular hypertrophy. This was believed to be due to the leftward position of the enlarged heart with the apex in the mid-axillary line so that the electrode at V_6 was closer to the heart than at V_5. Patients with midanterior myocardial infarctions were excluded, since they normally are expected to have higher R waves in the lateral leads that are at the same time farther from the site of injury. Despite these exclusions, the finding of RV_6 greater than RV_5 was present in 51 patients (25.5 per cent of the whole series) with known left ventricular hypertrophy. This number is comparable to that in which abnormal voltage criteria are met and would appear, therefore, to have equal diagnostic importance.

Discussion

This study reemphasizes the shortcomings of the scalar electrocardiogram in determining the presence or absence of left ventricular hypertrophy by the use of any single criterion or, indeed, by the application of several criteria. The electrocardiogram can, in fact, be entirely normal in the presence of severe left ventricular hypertrophy, as was demonstrated in 15 per cent of patients in this series. The presence of Sokolow's criteria of abnormal QRS voltage apparently correlates well with the demonstration of left ventricular hypertrophy at autopsy.[1] However, the absence of abnormal QRS voltage criteria in no way assures that severe left ventricular hypertrophy will not be found at postmortem examination. If these criteria were adhered to, the diagnosis of left ventricular hypertrophy by electrocardiogram could have been made in only 22 per cent of the patients in this group. Or, if those cases are excluded who demonstrated myocardial infarction or bundle-branch block (63 cases), the diagnosis by abnormal voltage would have been appar-

ent in 32 per cent of the remainder. Some of the factors that obviated abnormal QRS voltages are readily explainable (e.g., myocardial infarction and bundle-branch block). Other situations in which severe left ventricular hypertrophy occurred without abnormal QRS voltages, are not so easily explained (e.g., normal electrocardiogram, serial tracings with and without abnormal QRS voltage, and diffuse myocardial disease with no specific electrocardiographic abnormalities).

The electrocardiographic finding of the classical ST-T change, which has been attributed to left ventricular hypertrophy, was the most reliable criterion for the diagnosis of left ventricular hypertrophy in this series (table 1). It was present, however, in only 55 per cent of the group. Here again, both myocardial infarction and intraventricular block often altered the S-T segments and T waves in such a fashion that left ventricular hypertrophy could not be diagnosed. When those electrocardiograms showing frank myocardial infarction and bundle-branch block were rejected, the ST-T abnormalities of left ventricular hypertrophy were found in 80 per cent of the remaining 137 patients.

The fact that 51 patients out of 200 showed a taller R wave in V_6 than in V_5 may be of some diagnostic importance. This finding is, of course, significant of hypertrophy only in the absence of a mid-anterior myocardial infarction in which the lateral wall of the left ventricle has been spared.

The intrinsicoid deflection was measured in all electrocardiograms in this series and, although such measurements may at times be helpful in the diagnosis of left ventricular hypertrophy, consistent abnormalities were not found.

The criticism might be advanced that this series is loaded with too many abnormalities that interfere with abnormal QRS voltages and other criteria used in the electrocardiographic diagnosis of left ventricular hypertrophy. However, this group of 200 autopsied patients with proved left ventricular hypertrophy is consecutive and believed to be entirely representative of the variety and kind of abnormalities normally encountered in cardiologic practice.

The electrocardiogram is but one diagnostic means, albeit one of the best, for the determination of disorders of the heart. It often provides the first and occasionally the sole clue to the presence of ventricular enlargement. It would seem unwise, therefore, to limit its diagnostic worth by linking it to a special criterion with a low index of specificity. When abnormal voltage requirements are met, hypertrophy is almost certainly present. However, left ventricular hypertrophy must not be excluded when presently accepted electrocardiographic criteria are not fulfilled.

Summary

The antemortem electrocardiograms of 200 consecutive patients with autopsy-proved left ventricular hypertrophy were studied, and correlations were made with the anatomic findings. Special attention was given to the presence or absence of abnormal QRS voltage criteria to determine their validity and specificity in left ventricular hypertrophy.

The shortcomings of the scalar electrocardiogram in determining the presence or absence of left ventricular hypertrophy by the use of any single criterion or, indeed, by the application of several criteria, are reemphasized.

The absence of abnormal QRS voltage criteria in the electrocardiogram is highly unreliable in dismissing left ventricular hypertrophy as a diagnostic possibility.

The reliability of the presently accepted electrocardiographic signs of left ventricular hypertrophy is discussed, and the factors that commonly alter their reliability are considered.

The characteristic ST-segment and T-wave changes associated with left ventricular hypertrophy probably remain the most reliable electrocardiographic sign available; however, ST-T changes of the left ventricular hypertrophy type were present in only 55 per cent of patients in this series. If patients with obvious myocardial infarction or bundle-branch block are excluded, ST-T changes were seen in 80 per cent of the remainder.

In the absence of midanterior myocardial infarction the finding of a taller R wave in V_6 than the R wave in V_5 may be a helpful hint as to the presence of left ventricular hypertrophy.

Abnormally high voltage of the QRS complexes was found in 22 per cent of the whole group or 32 per cent when frank myocardial infarction and bundle-branch block were excluded. Abnormally high voltage as the sole manifestation of left ventricular hypertrophy was exceedingly rare in this series.

ACKNOWLEDGMENT

The author expresses his gratitude to Dr. Conger Williams, Massachusetts General Hospital, Boston, Mass., and to Dr. David Littmann, U.S. Veterans Hospital, West Roxbury, Mass., for their kind advice and encouragement in the preparation of this work.

SUMMARIO IN INTERLINGUA

In 200 casos consecutive de hypertrophia sinistro-ventricular con confirmation necroptic, le electrocardiogrammas de ante morte esseva studiate e correlationate con le constatationes anatomic. Attention special esseva prestate al presentia o absentia de criterios de anormalitate del voltage de QRS con le objectivo de determinar lor validitate e specificitate in hypertrophia sinistro-ventricular.

Le imperfectiones del electrocardiogramma scalar in determinar le presentia o absentia de hypertrophia sinistro-ventricular per le uso de un sol criterio o, de facto, de un combination de plure criterios es sublineate de novo.

Le absentia de criterios de anormalitate del voltage de QRS in le electrocardiogramma es un base multo incerte pro rejicer hypertrophia sinistro-ventricular como possibilitate diagnostic.

Es discutite le fidelitate del currentemente acceptate signos electrocardiographic de hypertrophia sinistro-ventricular. Le factores que communmente affice ille fidelitate es considerate.

Le alterationes characteristic del segmento ST e del unda T que occurre in association con hypertrophia sinistro-ventricular remane probabilemente le plus fidel signos electrocardiographic que existe. Tamen, alterationes de ST-T del typo characteristic de hypertrophia sinistro-ventricular esseva presente in solmente 55 pro cento del patientes in le presente serie. Quando le patientes con obvie infarcimento myocardial o bloco de branca es excludite, le proportion del casos con alterationes de ST-T monta a 80 pro cento.

In le absentia de infarcimento myocardial centro-anterior, le constatation que le unda R in V_6 es plus alte que in V_5 es possibilemente un indicio de valor con respecto al presentia de hypertrophia sinistro-ventricular.

Anormalmente alte voltages del complexes QRS esseva trovate in 22 pro cento del gruppo total e in 32 pro cento post exclusion del casos de franc infarcimento myocardial e bloco de branca. Anormalemente alte voltages como sol manifestation de hypertrophia sinistro-ventricular esseva excessivemente rar in iste serie.

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Demonstration of Muscle Sphincters as a Capillary Component in the Human Heart

By D. Vincent Provenza, Ph.D., and Sidney Scherlis, M.D.

The capillary network in the ventricular myocardium in man consists of 2 sphincter-type capillaries (the *metarteriole* and the *precapillary*) and a nonmuscular capillary, the classic or *true capillary*. The muscular components of the metarterioles and of the precapillaries are innervated by nerve fibers of which the terminal structure ends as a knotted fibrillar process near the muscle nucleus. The sphincter capillary and its nerve constitute a functional unit. These structures are encountered in the myocardium of man more frequently than elsewhere. In man these functional units conceivably may play a much more prominent role than heretofore realized in the dynamics of cardiac vascularization.

ATTENTION has been focused on coronary circulation for several decades and, although the general paths of circulation have been adequately established, knowledge concerning the specific details of capillary circulation and types of vessels in the human heart still leaves much to be desired. Wearn's[1] investigation of the coronary capillaries was of a quantitative nature in which he attempted to determine the relative number of these structures in the normal heart as opposed to the number in the abnormal failing heart.

Studies of capillary vessels in fixed preparations and in vivo have revealed that this system is not composed solely of one type. Although capillary variants have been demonstrated in a variety of organs, their location and distribution appear to be correlated with their functional activity. The structural pattern of the capillary system in mesenteric capillary circulation,[2] in the pulps of human teeth,[3] and in the dog's heart[4] consists of a thoroughfare channel that is subordinate to the metarteriole. The latter may communicate with either a precapillary or a true capillary. Arteriovenous anastomoses have been observed to join arterioles or metarterioles with venules.

If the capillary variants that have been observed in the dog's heart could also be demonstrated in the myocardium of man, the dynamics of coronary circulation in the normal and diseased states might be better understood. It is the purpose of this paper to discuss the capillary circulation of the human heart from a point of view heretofore not considered.

Material and Methods

Hearts were obtained at autopsy within approximately 1 hour after death to reduce the possibility of postmortem changes. Tissues were fixed in 5, 5, 8, and 10 per cent aqueous solutions of formalin successively for 3 hours each.. The tissues were kept in 10 per cent formalin for an additional 48 hours; then they were washed in running tap water, dehydrated by the usual alcohol series, cleared in xylene, and embedded. The sections were cut 5 μ thick and were arranged serially on coded slides. The Lillie-Pasternack[5] method was used to stain the muscle components of the tissue and on alternate slides the Bodian[6] method was employed to demonstrate nerve endings. Trials with fixation in only 10 per cent formalin demonstrated appreciable tissue distortions, which were not found when gradual fixation was employed. Sections of hearts kept in 0.9 per cent saline solution for intervals of 3 hours or more before fixation in 10 per cent formalin demonstrated postmortem changes that progressed rapidly and proportionally with time after the initial period of 3 hours.

Results

The larger arteries that are found superficially on the myocardium anastomose freely with some of the daughter vessels invading the substance of the heart tissue. These vessels that enter the substance of the myocar-

From the Department of Histology and Embryology, Baltimore College of Dental Surgery, Dental School, and the Department of Medicine, School of Medicine, University of Maryland, Baltimore, Md.

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dium carry with them a rather dense areolar connective tissue in which are located the accompanying veins and nerves. Ganglionic masses are observed in this dense connective tissue of the ventricular myocardium. As the arteries travel through the tissue and bifurcate, they decrease in diameter; simultaneously the connective tissue in which they travel becomes progressively less dense. The rapidity with which the caliber becomes lessened varies with the different daughter vessels and their ultimate function. In those vessels that act primarily to transport blood through the tissues, the diameters decrease gradually; in those that vascularize the adjacent area, the diameters are reduced with great rapidity and they terminate in a capillary network.

The arterioles are characterized by an intima, which consists of an endothelial lining and a thin delicate subendothelium with an internal elastic membrane rarely in evidence. The media consists of a continuous layer of muscle generally 1 cell in thickness (fig. 1). The adventitia of these vessels is composed of a looser type of areolar connective tissue. When the size of a terminal arteriole is reached, the characteristics of the media begin to change. The continuous layer of muscle, so characteristic of the media of arterioles and larger vessels, becomes discontinuous. With this loss of continuity of the muscular coat, these vessels can no longer be considered arterioles but metarterioles (figs. 2 to 4). The sphincters associated with the metarterioles are in the form of minute circumferentially arranged muscle bands composed of 1, 2, or 3 cells, which function as a unit. These are usually found in pairs (rarely more than 3) in that portion of the metarteriole which communicates with the parent arteriole. However, as the distance from the parent arteriole is increased, not only are the sphincters reduced in numbers, but the distance between sphincters is increased (fig. 3). Although the sphincter unit, which is made up of a greater number of muscle cells, is generally located closer to the parent vessel, this need not always be the case (fig. 4). Metarterioles are observed in which a unit of as many as 3 muscle cells is found between individual muscle units.

The precapillaries found in the human heart may arise as a bifurcation either of a metarteriole or of an arteriole. At the segmental area of attachment with the parent vessel, the precapillary possesses muscle cells, herein termed the precapillary sphincter (fig. 5). The number of muscle cells comprising the sphincter in this type of capillary varies again from 1 to 3. The portion of the precapillary distal to the sphincter is indistinguishable from a true capillary, since its sole composition is endothelial.

The sphincters that are found in the metarterioles or the precapillaries are identical in position and in their anatomic features with the muscle cells, which comprise the media of the larger vessels (arteries or veins).

Arteriovenous anastomoses are observed in the ventricular myocardium (fig. 6). These vessels, which act as shunts bypassing all or some of the capillarial circulation, are herein demonstrated to connect arterioles with venules or metarterioles with venules. The walls of these vessels may vary in their degree of musculature depending upon whether the parent vessel is an arteriole or a metarteriole. The segment of the arteriovenous anastomosis communicating with an arteriole is considerably more muscular than a segment of comparable location attached to a metarteriole. The portion of the arteriovenous anastomosis, intervening between the points of attachment from artery to vein, decreases in its musculature as the distance from the parent vessel is increased. This reduction may range from an occasional individual muscle to total absence.

The true capillaries found in the human heart consist of an endothelial tube completely devoid of muscular components. Although these vessels are generally oriented parallel to the long axis of the cardiac fibers, some capillaries are noted to run obliquely or less often at right angles to the myocardial muscle fibers.

The capillaries anastomose so profusely among the cardiac fibers that an individual fiber may have several true capillaries asso-

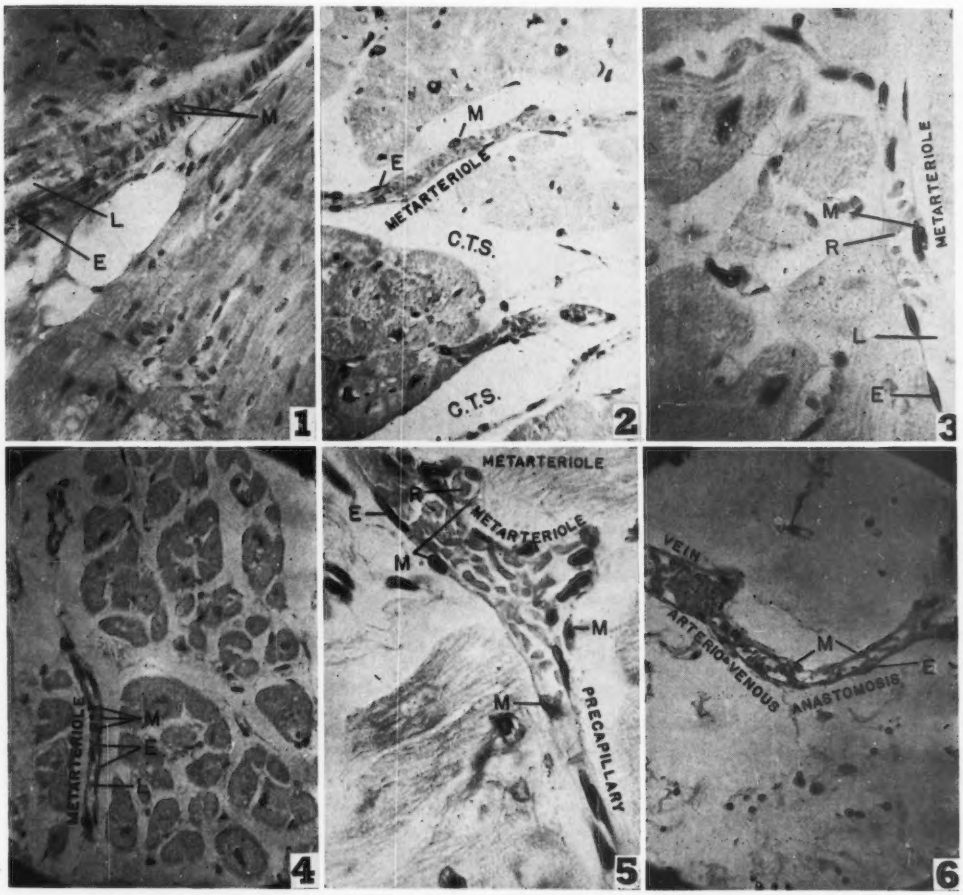

FIG. 1. Arteriole of ventricular myocardium. Note continuous muscle layer. *M*, muscle nucleus; *L*, lumen of vessel; *E*, endothelial nucleus. Romanowsky, 5 μ, × 400.

FIG. 2. Metarteriole of ventricular myocardium in connective-tissue septa (C.T.S.). *M*, muscle nucleus; *E*, endothelial nucleus. Romanowsky, 5 μ, × 140.

FIG. 3. Metarteriole at right angle to muscle fibers of ventricular myocardium. *L*, lumen of the vessel; containing *R*, erythrocytes; *M*, nucleus of muscle sphincter; and *E*, endothelial nucleus. Romanowsky, 5 μ, × 900.

FIG. 4. Metarteriole of ventricular myocardium showing 3 muscle cells making up the sphincter. *M*, muscle nuclei; *L*, lumen of the vessel; surrounded by, *E*, endothelial cells. Romanowsky, 5 μ, × 400.

FIG. 5. Precapillary branching from metarteriole. Precapillary sphincter consisting of 2 muscle cells, *M*. Note smaller metarteriole with endothelial nucleus, *E*, bulging into lumen containing erythrocytes, *R*.

FIG. 6. Arteriovenous anastomosis. Note that segment of vessel distal to vein is more muscular, as evidenced by muscle nuclei, *M*. Romanowsky, 5 μ, × 140.

ated with it. Although branching of the pillaries into 2 daughter vessels is the general rule, trifurcation is not uncommon.

Nerve fibers accompanying the vessels of calibers are herein demonstrated. The larger nerve trunks travel with the larger vessels in the areolar connective-tissue septa of the heart. The branching of the larger nerve trunks is associated with the partitioning process of the connective tissue that invades

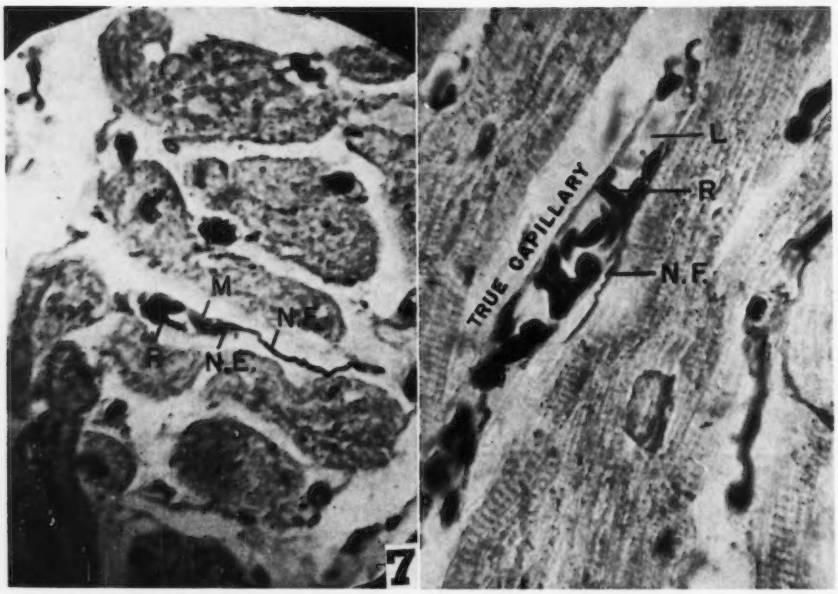

FIG. 7. Metarteriole showing muscle nucleus, *M*, in intimate association with nerve ending, *N.E.*; nerve fiber, *N.F.* Bodian, 5 μ, $\times$ 900.

FIG. 8. True capillary containing erythrocytes, *R*, within its lumen, *L*, and showing nerve fiber, *N.F.* Bodian, 5 μ, $\times$ 900.

the myocardium. The smaller nerve trunks that result from progressive subdivisions run in close proximity to the capillary system. At intervals, a nerve fiber which remains proximally attached to the parent fiber is extruded. This daughter fiber travels to the muscle sphincter of the metarteriole or precapillary with which it is associated or it may be associated with an adjacent vessel. Prior to intimate association with the muscle cell, the nerve fiber becomes splayed. The fibrillar process thus formed surrounds the muscle cell, so that the knotted ends terminate in the region of the nucleus (fig. 7). Although nerve fibers travel along with true capillaries, no association between the endothelial cells and these fibers is observed (fig. 8).

The sphincters of the metarterioles and precapillaries are found in both the relaxed and the contracted conditions. In the relaxed state, the muscle nuclei are ovoid and somewhat elongated when viewed from the surface. This condition is reflected in the underlying endothelial cell and the lumen of the vessel. The nucleus of the endothelial cell is greatly elongated and appears laterally compressed (fig. 4). The lumen of the muscular capillary appears to be normal in that it is symmetrically round (no inward bulging of the endothelial nuclei).

In the contracted condition, the muscle nuclei of the sphincter ed capillaries appear broadly ovoid (surface view). The underlying endothelial cells are altered in diameter, their nuclei become rounded to the point that they protrude into the lumen, which has become constricted at this point. The degree of luminal constriction is contingent upon the intensity of contraction. The endothelial cells between sphincters in the metarterioles and the endothelial cells immediately distal to the precapillary sphincters appear to be identical with the endothelium underlying the sphincters in the relaxed condition. In the contracted condition of the sphincter, however, the endothelium underlying the sphincter and that portion between sphincters appear to be different. The endothelium un-

er and that immediate adjacent to the muscle ell are affected as described above. Since he intervening portion is not involved, it ears the same characteristics as that in the elaxed condition.

The segments between sphincters of the netarteriole and that distal to the precapillary sphincter are the same in composition as he true capillary. Because of this similarity n structure, positive identification can be ascertained only if the vessels are longitudinally disposed or if the sections are serially studied and reconstructed.

Discussion

The anatomic structure of the larger arterioles in the myocardium was observed to be more or less consistent with that found in other parts of the body except that an internal elastic membrane is rarely seen. The primary function of this membrane is to give support and strength to the walls of the vessel. In the myocardium of man, and especially in the ventricular myocardium, the walls of these vessels are greatly reinforced by the surrounding muscle tissue. It is not inconceivable that the internal elastic membrane of arterioles in this part of the heart should be at best very poorly developed or even totally wanting.

With the demonstration of the capillary variants in the pulps of human teeth[3] and in the myocardium of the dog[4] and with the command of the contractibility of these structures by various chemical and physical means,[7, 8] interest was aroused in a similar capillary network in the human heart. Unless he tissue is obtained immediately after death nd is fixed gradually, postmortem changes n the appearance of the capillaries and nerve bers are effected. Rapid fixation results in ssue distortion which renders the demonstran of these structures extremely difficult if t impossible.[4]

The sphincters of the metarteriole and precapillary are identical in structure with their counterpart in the myocardium of the dog. hese are also identical with the muscle cells at are associated with the other vessels (arteries and veins) of the body except for those associated with the human dental pulp. The nuclei of the muscular components of all vessels of the radicular and coronal pulps are characterized by chromatin material that appears finer and consequently stains more hypochromatically than these structures in other vessels of the body.[3]

Although there appears to be no qualitative difference between the capillary sphincters in the myocardium of dog and of man, one conspicuous observation was made: the frequency with which the metarterioles, precapillaries, and the arteriovenous anastomoses are encountered in the ventricular tissue of man greatly exceed that found in the dog. Furthermore, while most of the capillary variants in the myocardium of dogs are located between the cardiac muscle fibers, in man, these structures are not restricted in their location but are found in the looser connective tissue septa as well. Finally, while the true capillaries in the dog are characterized by dichotomous branching resulting in 2 daughter capillaries of equal diameter, in man trifurcation as well as bifurcation of these vessels is present.

The metarterioles and precapillaries in the myocardium of man were observed in the constricted and in the dilated conditions; these are correlated with their association with nerve endings. There has been some controversy about the precise ramification of autonomic efferent fibers associated with blood vessels, heart, and other visceral structures. Some investigators postulate that the end structures of these nerves terminate in the nuclear region of the muscle cell; others report that the nerve-end apparatus, which may be in the form of bulbs, loops, or free endings, terminates either intercellularly or intracellularly; still others maintain that the beaded fibrillar end-process of the nerves terminate as syncytially arranged plexi enveloping individual muscle cells.[9] Our results[3, 4] corroborate those of the other investigators who have reported the knotted fibrillar processes. Furthermore, evidence supporting the existence of a terminal reticulum was not obtained.

The true capillary, which is solely endothelial in nature and hence is completely wanting in muscle cells, has not been demonstrated to have associated with it the knotted fibrillar processes characteristic of the sphincters of the metarterioles and the precapillaries.[4, 8] It is quite possible that, where nerve-end apparatus has been reported associated with endothelial cells,[10] the vessels in question were not true capillaries but sphincter capillaries.

Capillary occlusion effected by the endothelial cells, as reported by Midsuno[11] and by Sanders et al.[12] was not interpreted by Chambers and Zweifach[2] and by Kahn and Pollak[13] to result from the intrinsic action of the endothelial cell but from the contraction of the sphincters of the metarterioles and the precapillaries. Our studies tend to substantiate the interpretation of Chambers and Kahn and their associates, for no evidence of capillary constriction was observed in those vessels of the dental pulp,[4, 8] nor in the myocardium of dogs,[7] which are wanting in muscular components. This condition is also found to be characteristic of those portions of the muscular capillaries intervening between sphincters.

Qualitative differences in the capillary components on the one hand and the density of vessels in the myocardium on the other, would strongly suggest that cardiovascular dynamics play a far more important role in the functional processes of this organ than has been realized. Chambers and Zweifach[2] were able to produce changes in the diameter of the vessels when epinephrine and histamine solutions were dropped on the omentum of the dog and rat. Provenza and Biddington[8] effected marked vasodilatation and vasoconstriction of the sphincter capillaries of the radicular and coronal pulps of man when nitroglycerin and epinephrine, respectively, were topically applied. Identical results were produced with the intracardiac administration of drugs.[4, 7] The pharmacologic control of the circulation through the vessels of the capillary system emphasizes the importance of the capillary system in considerations of treatment of cardiovascular diseases.

Summary

Sphincter capillaries are components of the capillary bed in the ventricular myocardium of man. The ventricular myocardium is vascularized by a capillary bed consisting of 3 types of vessels. The *metarteriole* is a vessel of the same caliber as the true capillary. It is differentiated from the latter in that at varying intervals 1 or several muscle cells make up a sphincter unit. Although the larger sphincter units are found more proximally located to the parent vessels, this condition need not be true for all metarterioles. The *precapillary* is the same anatomically as the true capillary except that at the segmental area of an attachment with the parent vessel (metarteriole or arteriole) a sphincter consisting of 1 to 3 muscle cells is found. The *true capillary* consists of a simple endothelial tube.

Arteriovenous anastomoses are found in the ventricular myocardium of man. These are vessels that act as shunts, bypassing some or all of the capillary types. The arteriovenous anastomosis may connect an artery with a vein or a metarteriole with a vein. The anatomic distinction between parent origin (artery or metarteriole) is made on the basis of the degree of musculature present in the wall of the arteriovenous anastomosis.

The sphincter and its nerve-end apparatus constitute a functional unit. Nerve fibers are located in close proximity to the capillary types. At varying intervals, daughter nerve fibers divorce themselves from the parent trunk and travel to the muscle sphincter of the metarteriole or precapillary with which it is associated or to adjacent vessels. These fibers terminate as fibrillar processes in the nuclear region of the cell. True capillaries have not been demonstrated to have nerve-end apparatus associated with them.

Acknowledgment

Appreciation is expressed to Myron S. Aisenberg, Dean and Professor of Pathology, for valuable contributions and, for photomicrographs, to Claude P. Taylor, Director of the Department of Visual Aids, Baltimore College of Dental Surgery, Dental School, University of Maryland.

Summario in Interlingua

Capillares con sphincteres es componentes del vasculatura capillar in le myocardio ventricular del homine. Le myocardio ventricular es alimentate per un vasculatura capillar que consiste de 3 typos de vasos. Le *metarteriola* es un vaso del mesme calibre como le ver capillares. Illo se distingue per le presentia, a varie intervallos, de mechanismos sphincteric consistente de 1 o plure cellulas muscular. Ben que le plus grande mechanismos sphincteric se trova generalmente in sitos plus proxime al vaso parente, iste condition non prevale necessarimente in omne metarteriolas. Le *precapillares* es anatomicamente le mesmo como le ver capillares, excepte que in le area segmental del attachamento al vaso parente (que pote esser un metarteriola o un arteriola) un sphincter se trova que consiste de 1 a 3 cellulas muscular. Le *ver capillares* consiste de simple tubos endothelial.

Anastomoses arterio-venose se trova in le myocardio ventricular del homine. Istos es vasos que age como shunts saltante plures o omnes del typos capillar. Le anastomoses arterio-venose pote connecter un arteria con un vena o un metarteriola con un vena. Le differentiation anatomic secundo le vaso parente—arteria o metarteriola—se face secundo le grado de musculatura presente in le pariete del anastomosis arterio-venose.

Le sphinctere e su apparato de termino nerval constitue un unitate functional. Fibras nerval de ordine filial se distacha a varie intervallos ab le trunco parente e viagia al sphincter muscular del metarteriola o del precapillar con que illos es associate o a un vaso adjacente. Iste fibras se termina como processos fibrillar in le region nuclear del cellula. In ver capillares, nulle associate presentia e apparato de termino nerval ha unquam essite demonstrate.

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Effects of Intravenous Administration of Fibrinolysin (Plasmin) in Man

By KENNETH M. MOSER, M.D.

The potentiality of dissolving clots has aroused great interest in fibrinolysin (plasmin) as a therapeutic agent in thromboembolism. In this paper the effects of intravenous administration of purified fibrinolysin in man are reported, with special emphasis upon systemic toxicity and alterations in clotting factors and fibrinolytic activity. This information is necessary for the evaluation of this agent for clinical purposes.

SINCE no adequate methods presently exist for detecting the presence of a "prethrombotic" state, the physician must unfortunately deal with thromboembolic disease when it reaches an overt, symptomatic phase. The most effective therapy at this juncture would include a combination of agents that could ensure both prompt dissolution of existing thrombus and prevention of new thrombosis.

Although heparin has some capacity to accelerate the process of clot dissolution in vivo, none of the anticoagulant drugs adequately satisfies this combined requirement.[1-3] Therefore, much recent effort has been devoted to the development of agents that might dissolve intravascular clot acutely.

The therapeutic feasibility of induced clot lysis was suggested by discovery of the intrinsic fibrinolytic activity of plasma, which resides in the plasminogen-plasmin (profibrinolysin-fibrinolysin) system. It appears likely that this lytic system is constantly functioning within the body to remove unwanted fibrin deposits.[4] Unfortunately this normal mechanism rarely acts with sufficient speed and intensity to prevent the sequelae of extensive occlusion in large vessels. Therefore, various attempts are currently being made to achieve rapid thrombolysis with materials that can acutely enhance the fibrinolytic activity of plasma.

From the Enzyme Research Laboratory, District of Columbia General Hospital; and the Department of Medicine, Georgetown University Medical School, Washington, D. C.

The proteolytic enzyme trypsin, the bacterial derivative streptokinase, and certain protein-free bacterial pyrogens have all been utilized to dissolve intravascular thrombi. While trypsin in vitro is both directly fibrinolytic and capable of activating profibrinolysin,[5] attempts to achieve clot lysis with intravenous trypsin have met with infrequent success.[6-8] Furthermore, the enzyme has such a broad spectrum of proteolytic action that its intravenous administration may lead to serious depletion of plasma coagulation factors.[6, 8, 9]

Streptokinase has no direct fibrinolytic activity. Rather, it serves as an activator of profibrinolysin, either directly or by converting a plasma pro-activator to activator.[10, 11] Intravenous streptokinase can produce clot lysis in the experimental animal,[12] and doses of sufficient size can considerably increase fibrinolytic activity of human plasma.[13-15] Unfortunately, a significant portion of the population, by virtue of prior streptococcal infection, may exhibit antistreptokinase activity in the plasma.[16] The presence of such antibodies not only raises the possibility of allergic responses,[17] but may also play a role in the inconsistency with which well-tolerated doses of streptokinase enhance plasma fibrinolytic activity.[13-15]

The fibrinolytic potential of the pyrogenic bacterial lipopolysaccharides in vivo has been explored by von Kaulla.[18, 19] These materials do not exhibit fibrinolytic activity in vitro. The mechanism by which they induce such activity in vivo is uncertain, but present

e dence suggests that they act by releasing l sminogen activators from some endogenous s rce. Such nonenzymatic activation of the l sma fibrinolytic mechanism is a promising d velopment in the effort to find a satisfac- t y, clinically useful thrombolytic agent.

While both streptokinase and bacterial l rogens hold considerable promise as effec- t e thrombolytic materials, their indirect m ode of action and dependence upon the s pply of plasminogen in the plasma have cer- t in practical and theoretical disadvantages. Therefore, other investigators have explored the possibility that fibrinolysin itself, isolated from the human plasma, might prove a more direct and controllable agent for increasing plasma fibrinolytic activity. This possibility has recently become subject to experimental proof by the development of a highly purified preparation of fibrinolysin suitable for clinical study.[20, 21] Extensive in vitro and animal studies with this material have demonstrated several characteristics that render it promising as a therapeutic agent in human thromboembolic disease. Fibrinolysin rapidly dissolves fibrin clot in vitro and exerts similar effects upon extravascular fibrin coagulum in vivo.[22] The intravenous infusion of fibrinolysin in experimental animals has consistently led to dissolution of artificially produced arterial and venous thrombi.[23-25] Although the enzyme does exhibit proteolytic activity in vivo, fibrin and its close structural relative fibrinogen appear to provide the major substrates in plasma.[24-27] Such preferential action may be related not only to the protein structure of these substances but also to the adsorptive affinity of fibrin for fibrinolysin.[4, 11] Finally, the intravenous infusion of fibrinolysin in animals has been attended by minimal evidence of allergic potential or other toxicity.[23, 26] Preliminary reports indicate that the experimental data regarding the value and low toxicity of fibrinolysin may apply to man.[28, 29]

Detailed study of the toxicity, duration of action, and dosage-response characteristics of fibrinolysin is important, for experience with trypsin and streptokinase has indicated that human responses to enzymatic agents often are not accurately predicted from in vitro or animal investigations. The present study was therefore undertaken to assess the coagulation changes, systemic toxicity, and fibrinolytic activity that follow intravenous infusion of highly puried fibrinolysin in man at various dosage levels. The data are derived from changes that followed 72 infusions of fibrinolysin in 63 patients.

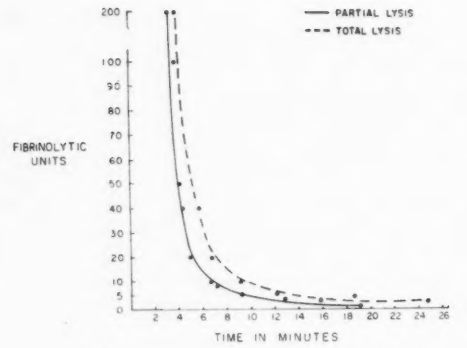
TABLE 1.—*Composition of Patient Group Receiving Fibrinolysin*

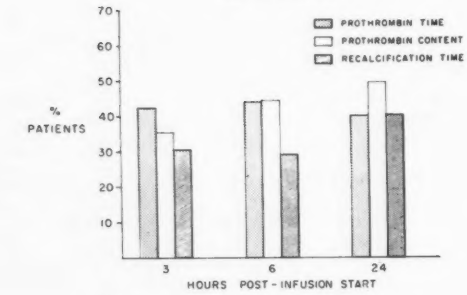
	Patients	Infusions
Active deep thrombophlebitis		
With pulmonary embolism	3	5
Without pulmonary embolism	14	15
Pulmonary embolism without obvious source	8	11
Superficial thrombophlebitis	7	7
Arterial thrombosis or embolism		
Cerebral thrombosis	12	13
Internal carotid thrombosis	2	3
Brachial embolus	1	2
Retinal artery thrombosis	1	1
Coronary thrombosis	1	1
Sickle-cell disease	1	1
No apparent thrombosis		
Carcinoma	9	9
Cellulitis	2	2
Miscellaneous	2	2
Total	63	72

MATERIALS AND METHODS

Study Group. The 63 patients in this study (table 1) were inpatients at the District of Columbia General Hospital between February and December 1957. They all had or were subject to threat of thrombosis. The patients were divided into 3 dosage groups: 19 infusions of 30,000 fibrinolytic units (F. U.) of fibrinolysin (group I); 28 infusions of 40 to 50,000 F. U. (group II); and 25 infusions of 69 to 90,000 F. U. (group III).

Determination of Fibrinolysin Dosage. The fibrinolysin was derived from the euglobulin fraction of human plasma as profibrinolysin by a modification of the method of Fishman and Kline.[21] Activation was achieved by addition of small amounts of purified streptokinase. After activation, procedures were carried out to remove the streptokinase, and the material was lyophilized. No capacity to activate plasminogen was detectable in the final product.





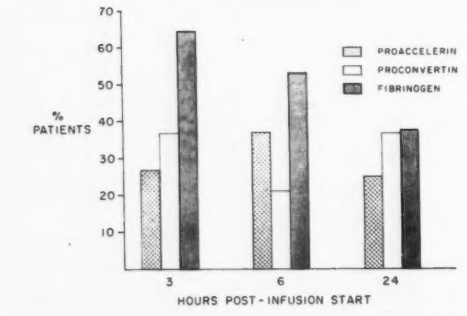


FIG. 1 *Top.* Standard curves relating fibrinolytic units to lysis time.

FIG. 2 *Middle.* Percentage of patients showing greater than 5 per cent prolongation of prothrombin time or recalcification time, or depression of prothrombin content following fibrinolysin infusion.

FIG. 3 *Bottom.* Percentage of patients showing greater than 5 per cent depression of proaccelerin, proconvertin, or fibrinogen following fibrinolysin infusion.

To assure standardization of the fibrinolysin and to allow other workers to compare their experience with ours, the following standardization procedure was carried out. Fibrinolysin* was supplied by the manufacturer initially in vials containing 25,000 "fibrinolytic units" per vial. This labeled unitage was determined by the supplier on the basis of assays employing both fibrin and non-fibrin test substrates. The initial lot of material supplied serves as the "house standard" and was assayed in our laboratory by a technic similar to that described by Loomis and co-workers.[30] Serial dilutions of the standard fibrinolysin material were prepared. To 0.1 ml. of the various fibrinolysin dilutions in a 13-by-100 mm. test tube were added 0.2 ml. of a freshly prepared 1 per cent solution of bovine fibrinogen (Armour) in imidazole buffer (pH 7.2) and 0.2 ml. of human thrombin in imidazole-saline-glycerine buffer solution (containing 4 units of thrombin), and the tube was placed in a water bath at 37 C. At 1 minute after the start of incubation and at 30-second intervals thereafter the tube was removed from the water bath and tilted gently to the horizontal position. A firm clot formed within the first 15 seconds of incubation. The clot remained firm during tilting for many hours if fibrinolysin was absent. In the presence of fibrinolysin, the clot softened and soon after moved freely down the test tube as it was tilted. This was chosen as the endpoint for "partial lysis." If the incubation period is extended, total lysis of the clot will occur. While there is a close correlation between the time required for partial and total lysis (fig. 1), the former was subject to a higher degree of reproducibility and therefore was chosen as the endpoint of the assay.

Lysis times differed significantly ($p < .01$) for the dilutions studied from 1 to 40 units. Differences in lysis times for 200 and 100 units, 100 and 50 units, and 50 and 40 units were not significant, but differences between 200 and 50 units were significant ($p < .01$).

The unitage of all subsequent lots of material was defined on the basis of this standard curve. While the standardization by the manufacturer and ourselves correlated well, the dosage in our studies was based on standardization of each new lot by our own assay. Before each infusion, the material was tested at several dilutions to assure that no alteration had occurred in fibrinolysin activity during storage at —20 C.

Method of Infusion. Immediately prior to infusion, 25,000 fibrinolysin units were dissolved in approximately 5 ml. of normal saline and added to 500 to 1000 ml. of 5 per cent dextrose in water. The infusion was introduced through ordinary plastic tubing over periods of 2 to 4 hours via an antecubital or forearm vein.

Blood Samples. Blood samples were drawn in all instances prior to and 24 hours following infu-

*Fibrinolysin was supplied for this study as Actase Fibrinolysin (Human) by the Ortho Research Foundation, Raritan, N. J.

sion. In 63 cases, samples also were drawn at approximately 3 and 6 hours after infusion; and in 9 others, at 6 hours only. Samples were collected with 0.1 M sodium oxalate as the anticoagulant and placed in ice at the time of withdrawal. Blood not used for hematocrit level or white blood count was immediately centrifuged, and the plasma was tested promptly or stored at —20 C.

Coagulation Studies. The 1-stage prothrombin time[31] and plasma recalcification time[31] were determined in all samples. In 36 cases, assays of prothrombin, proconvertin, and pro-accelerin by the methods of Lewis[32] and determination of fibrinogen by a modification of the method of Morrison, Edsall, and Miller[33] were also made. White blood counts and hematocrit levels (Wintrobe) were determined before and 24 hours following start of infusion in all patients.

Assay of Plasma Fibrinolytic Activity. This assay is identical to that described for establishment of the standard curve, with the exception that 0.4 ml. of the patient's plasma was substituted for the 0.1 ml. of fibrinolysin dilution. Thus, the test system consisted of plasma, fibrinogen, and thrombin.

To establish normal values for the assay, 245 control determinations were made (table 2). In addition, 18 patients were studied serially at 0, 3, 6, and 24 hours following start of an intravenous infusion of 1,000 ml. of 5 per cent dextrose in water (table 2). Finally, 20 hospitalized patients and 15 normal subjects were studied daily for 5 days (table 2).

These studies indicate the stability of lysis times by this method in serial samples over a 24-hour period and in daily samples.

On the basis of these control values, the assay was terminated after 30 minutes, and no patient with lysis time above 25 minutes was considered to have significant plasma fibrinolytic activity.

Calculation of increase of fibrinolytic activity was determined by the following formula:

$$\text{Per cent increase} = 100 \times \frac{(\text{Control lysis time}) - (\text{Lysis time at } x \text{ hours})}{(\text{Control lysis time})}$$

By definition, control lysis time cannot exceed 30 minutes.

During the investigation, all lysis times were determined in duplicate and the mean of the 2 was taken as the lysis time. The determinations showed a high degree of reproducibility (table 3). As might be expected, the difference between duplicate determinations tended to increase with longer times except that with a lysis time of 30 minutes or more, a repeat determination gave very similar results, indicating minimal or absent fibrinolytic activity.

TABLE 2.—*Control Assays of Plasma Fibrinolytic Activity*

	No.	Mean lysis time (min.)	S.E.
Single determinations			
Hospitalized patients	137	27.6	0.44
Normal subjects	108	29.0	0.43
Total	245	28.2	0.30

	Before infusion	3 hours	6 hours	24 hours
Serial 24-hour control samples				
Mean lysis time	27.0	28.2	29.5	29.2
Standard error	1.5	1.0	0.4	0.6

	Day 1	2	3	4	5
Daily determinations					
Hospitalized patients					
Mean lysis time	26.4	27.2	24.5	28.5	23.9
Standard error	1.5	1.2	2.2	0.8	2.2
Normal subjects					
Mean lysis time	28.5	29.1	28.9	30.0	30.0
Standard error	0.8	0.7	1.1	0	0

TABLE 3.—*Reproducibility of Duplicate Lysis Times*

Lysis time (min.) first determination	No.	Mean difference* between first and second determinations	S.E.
0- 5.9	45	0.5	0.1
6.0-10.9	61	1.0	0.2
11.0-15.9	38	1.2	0.2
16.0-20.9	37	1.6	0.3
21.0-25.9	13	1.4	0.3
26.0-29.9	10	2.8	0.3
30	87	0.1	0.1
Total	291	0.8	0.1

*Mean difference indicated here is average of all differences without regard to direction of difference.

Miscellaneous Laboratory and Clinical Studies. Temperature, blood pressure, and pulse were measured prior to infusion and every 2 to 4 hours for 24 hours thereafter. When any deviation from baseline values persisted after 24 hours, measurement was continued until baseline values were reached. A standard 12-lead electrocardiogram was obtained before and 24 hours following infusion in all cases. In 22 patients, electrocardiograms were also performed 3 to 10 hours following start of infusion. Intradermal skin tests were carried out with 0.1 ml. of a saline-fibrinolysin solution containing 30 F. U. in 27 patients prior to infusion.

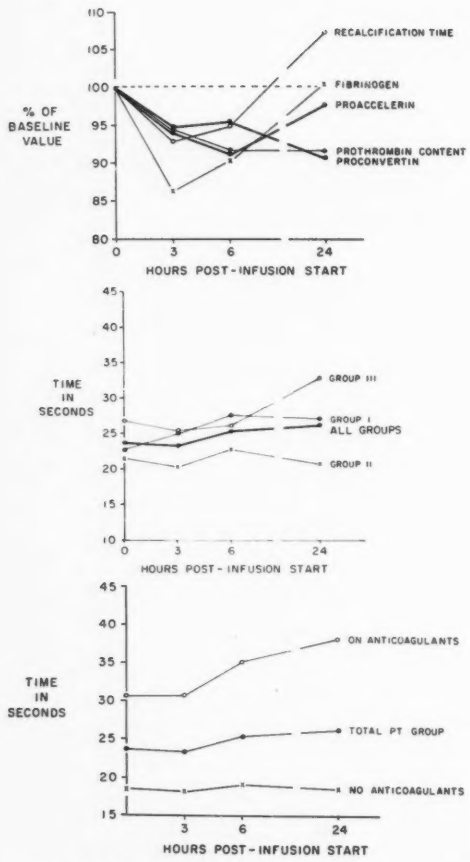


FIG. 4 *Top.* Degree of depression of various coagulation factors following fibrinolysin infusion.

FIG. 5 *Middle.* Average change in prothrombin time at intervals following fibrinolysin infusion, analyzed by dosage groups.

FIG. 6 *Bottom.* Average change in prothrombin time following fibrinolysin infusion, analyzed with reference to concurrent anticoagulant therapy.

Each patient receiving fibrinolysin was observed during and after infusion by the author and ward physicians. Evaluation continued throughout the hospital stay and in the out-patient clinic.

RESULTS

Changes in Coagulation Factors. The serial determinations of prothrombin time, prothrombin content, plasma recalcification time, proaccelerin content, proconvertin content, and fibrinogen content suggest that fibrinolysin does affect all of these coagulation factors.

TABLE 4.—*Average Percentage Change from Baseline Values of the Various Coagulation Factors at Each Time Interval Following Fibrinolysin Infusion*

	Hours after start of infusion 3	6	24
Prothrombin content			
Group I	– 2.5	– 5.1	– 5.1
Group II	– 9.0	–10.0	– 7.3
Group III	– 5.2	–11.0	–13.3
Total	– 5.4	– 8.5	– 8.4
Recalcification time			
Group I	– 9.7	–13.7	– 0.6
Group II	– 4.6	– 5.9	3.0
Group III	– 8.1	5.8	21.0
Total	– 7.0	– 5.1	7.5
Proaccelerin content			
Group I	– 7.8	–17.5	– 0.5
Group II	– 4.0	– 5.3	– 2.5
Group III	– 4.9	– 1.8	– 3.5
Total	– 5.7	– 8.6	– 2.2
Proconvertin content			
Group I	– 1.8	– 1.0	– 2.2
Group II	– 2.8	– 3.3	– 9.5
Group III	–12.0	– 9.9	–14.8
Total	– 5.5	– 4.5	– 9.1
Fibrinogen content			
Group I	–18.9	–15.7	–15.4
Group II	–13.8	– 2.3	6.7
Group III	– 9.4	–13.4	– 3.9
Total	–13.7	– 9.8	0.4

As indicated in figures 2 and 3, less than half the patients developed more than a 5 per cent depression (or prolongation in the case of prothrombin and plasma recalcification times) of any coagulation factor with the exception of the fibrinogen content. This was true at all intervals and at all dosage levels.

The *degree* to which depression (or prolongation in the case of prothrombin and plasma recalcification times) of these factors was produced following administration of fibrinolysin is presented in figures 4 to 6 and table 4. As can be seen, fibrinogen changed most, being decreased to 86.3 per cent of baseline values at 3 hours after start of fibrinolysin infusion.

TABLE 5.—*Incidence of Increased Fibrinolytic Activity after Infusion of Fibrinolysin**

	3 hours	6 hours	24 hours	Any time†
Group I	77	44	25	78
Group II	74	60	40	92
Group III	75	61	76	81
Total	75	56	48	84

*Enhanced activity defined as lysis time below 25 minutes and 10 per cent or more below baseline time.

†Evidence of enhanced fibrinolytic activity in at least 1 sample.

TABLE 6.—*Blood Pressure Changes after Infusion of Fibrinolysin*

	Maximum average decline Systolic (mm. Hg)	Diastolic (mm. Hg)	Per cent with 10 mm. Hg decline (systolic or diastolic)
Group I	4	5	11
Group II	9	10	25
Group III	16	10	36
Total group	10	7	24
Fever	17	12	42
No fever	4	3	15

While these data indicate that coagulation changes do follow fibrinolysin infusion, none of these changes differs significantly from baseline values. This lack of significance ($p > 0.05$) applies to the group as a whole and to the individual dosage groups with 1 exception. In the case of prothrombin at 24 hours in group III patients, a statistically significant prolongation is noted ($p < 0.05$). However, as indicated in figure 6, this prolongation appears to be related to the fact that anticoagulant therapy was begun in many of these patients coincident with fibrinolysin infusions. Separate analysis of data in patients who did and did not receive anticoagulants indicates that no statistically significant prolongation occurred in the latter group.

More important than the lack of statistically significant alterations is that none of these factors was depleted to a degree that is likely to impair the coagulative process.

Hemorrhagic Phenomena. No hemorrhagic phenomenon appeared in any patient who received fibrinolysin infusion, including 29 patients who were simultaneously receiving therapeutic doses of anticoagulant drugs. The series included 2 patients with advanced cavitary tuberculosis and recent hemoptysis; 4 patients with hemoptysis due to pulmonary embolism; 1 with bronchiectatic hemoptysis; 8 with moderate to severe hepatic cirrhosis; 1 patient 5 days following right upper lobectomy, and 1, 5 days after left brachial embolectomy. Postmortem examination in 9 patients who died within 2 weeks of the infusion disclosed no hemorrhagic foci in any organ that could be related to fibrinolysin administration.

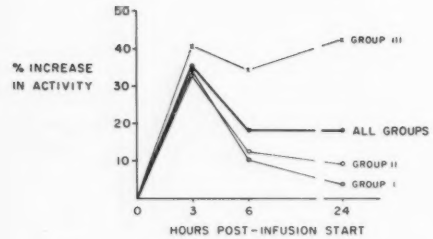
Hematocrit and White Blood Count. No significant changes occurred in hematocrit levels at 24 hours following infusion, the values being 36 per cent ± 8 at baseline and 35 per cent ± 8 at 24 hours. White blood count elevation exceeding 1,000 occurred at 24 hours following infusion in 38 per cent of all patients. The average elevation was 2,800 (range 1,200 to 9,800). Neither incidence nor degree of white count elevation correlated with fibrinolysin dosage, occurrence of fever, or degree of plasma fibrinolytic activity.

Fibrinolytic Activity. Enhanced plasma fibrinolytic activity* was demonstrable in at least 1 postinfusion sample in 84 per cent of all patients, including 78 per cent of group I, 92 per cent of group II, and 81 per cent of group III (table 5). Analysis by dosage groups indicates that, as dosage was raised, there was both prolongation and intensification of plasma fibrinolytic activity (fig. 7).

While the *incidence* of enhanced fibrinolytic activity was equally distributed among the 3 groups at 3 hours, groups II and III showed a higher incidence than group I at 6 hours. At 24 hours, group III showed an incidence of activity significantly greater than the other 2 groups.

The *intensity* of fibrinolytic activity also

*Based on control determinations and known errors of assays, a postinfusion sample with a lysis time that was less than 25 minutes and 10 per cent or more below baseline lysis time was taken as indicative of enhanced lytic activity.



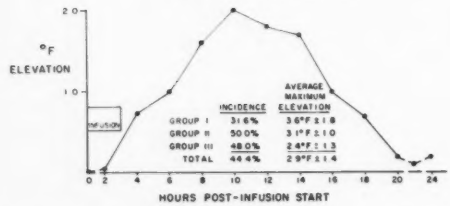


FIG. 7 *Top.* Enhancement of plasma fibrinolytic activity following fibrinolysin infusion, analyzed by dosage groups.

FIG. 8 *Bottom.* Composite curve of all febrile reactions following fibrinolysin infusion. Fever incidence and maximum temperatures are indicated beneath the curve.

appeared related to fibrinolysin dosage. At 3 hours, the average decrease in standard clot lysis time was 34.6 per cent in group I, 33.0 per cent in group II, and 40.9 per cent in group III. By 6 hours after infusion, groups I and II had declined to 10.8 and 12.8 per cent respectively, while group III patients still showed an average decrease in lysis time of 34.6 per cent. At 24 hours, clot lysis time was decreased by 3.7 and 9.8 per cent in groups I and II, while group III demonstrated a 42.1 per cent decrease.

Blood Pressures. Alterations in blood pressure following fibrinolysin infusion were minimal for the group as a whole, with the maximum decline averaging 10 mm. Hg systolic and 7 mm. Hg diastolic. Both the incidence and degree of blood pressure depression showed some tendency to increase as dosage was raised, but the differences between groups were not statistically significant (table 6).

The presence of fever was accompanied by an increased incidence and degree of blood pressure decline (table 6). A lowering of blood pressure exceeding 10 mm. Hg systolic or diastolic occurred in 42 per cent of patients with febrile reactions but in only 13 per cent without fever, a statistically significant difference. However, the differences in degree of blood pressure decline were not significant.

No instance of symptomatic hypotension occurred. Most of the blood pressure declines exceeding 10 mm. Hg systolic or diastolic occurred under 3 circumstances: during temperature elevation, in measurements made during the hours 12 p.m. to 8 a.m., and in patients with preinfusion blood pressure readings in the hypertensive range (above 140/90).

Temperature and Pulse. A febrile reaction was defined as any temperature elevation exceeding 1 F. that occurred during the 24 hours following infusion. Such responses occurred in 44 per cent of the total patient group.

Fever usually appeared 6 hours after start of infusion (range 3 to 14), reached its height at approximately 10 hours after infusion, and usually returned to normal within the next 10 hours (range 2 to 40) (fig. 8). In 5 patients temperature elevation persisted beyond 24 hours, and in 3 peak temperature elevation exceeded 4 F. (table 7).

Neither the incidence nor the degree of temperature elevation could be correlated with size of dose, rapidity of infusion, fibrinolysin skin tests, alterations in coagulation factors, or extent of fibrinolytic activity achieved. However, when patients were divided into 2 groups—those in whom extensive thrombotic material was clinically present and those in whom thrombotic material was minimal or presumed absent—a statistically significant correlation with fever ($p < .01$) was obtained (table 8).

Pulse changes tended to parallel temperature response and in no instance did a significant tachycardia (above 110) develop in the absence of a febrile reaction.

Electrocardiographic Changes. Electrocardiographic abnormalities appeared after infusion in 2 patients. A 79-year-old woman with arteriosclerotic heart disease and congestive heart failure developed atrial fibrillation 10 hours after infusion, and a 23-year-old man

with deep iliofemoral thrombophlebitis developed transient T-wave changes 6 hours after infusion. Both of these changes occurred near the peak of a febrile reaction.

Urinalysis. No significant changes in urinary sediment followed fibrinolysin infusion. In 12 instances, mild proteinuria was noted 24 hours after infusion, but it cleared by 48 hours. All patients with proteinuria had had febrile reactions.

Miscellaneous Observations. Nausea or chills accompanied approximately one third of the febrile reactions. Two patients vomited.

Two instances of apparent allergic skin reaction developed, both on the third day after infusion. One patient developed a hot, erythematous, pruritic reaction at the site of infusion, and the second patient developed a pruritic macular eruption over the extremities and the lower trunk, in addition to a similar but less severe reaction at the infusion site. Both reactions responded to local and antihistaminic therapy within 72 hours. In both cases a moderate fever (100 to 101 F.) developed and an erythematous spot appeared at the site of an intradermal fibrinolysin skin test originally recorded as negative. In 1 patient, a strong allergic history was present. In neither of these cases had subcutaneous infiltration of fibrinolysin occurred.

Subcutaneous infiltration of 5 to 20,000 F. U. inadvertently occurred in 7 patients. No adverse effects were noted other than what might be expected to follow infiltration of comparable amounts of dextrose solution.

Two patients developed unexplained episodes of epigastric pain near the peak of febrile reactions to infusion. The episodes were promptly terminated by meperidine and did not recur. Investigation revealed no cause for the pain in either case.

TABLE 7.—*Maximum Temperature Elevations Following Infusion*

Maximum elevation	No. patients	Per cent patients
0—1 F.	40	56
1—2 F.	11	15
2—3 F.	9	13
3—4 F.	9	13
Above 4 F.	3	4

TABLE 8.—*Incidence of Fever According to Presence of "Major" or "Minor" Thrombotic Disease*

	Infusions	Fever
"Major" thrombotic disease*		
Acute deep thrombophlebitis	20	13
Pulmonary embolism	11	6
Superficial thrombophlebitis	7	4
Total	38	23(61%)
"Minor" or no thrombotic disease*		
Cerebral thrombosis	13	4
Internal carotid thrombosis	3	1
Coronary thrombosis	1	0
Brachial artery embolus	2	1
Retinal artery thrombosis	1	0
Sickle-cell anemia	1	1
Carcinoma	9	1
Cellulitis	2	1
Miscellaneous	2	0
Total	34	9(27%)

*Major and minor apply to the extent of thrombotic material present, not to the functional consequences of occlusion.

DISCUSSION

Significant toxicity of intravenous fibrinolysin in man, at the dosage levels employed in this study, appears limited to its pyrogenic potential. The etiology of this pyrogenicity has not yet been defined. Three explanations might be advanced: (1) profibrinolysin itself is pyrogenic; (2) the fibrinolysin preparation used may contain pyrogenic residuals of streptokinase or of other materials introduced during the process of activation; (3) the actions of fibrinolysin within the body incite temperature elevation.

The first explanation does not appear tenable. Profibrinolysin is not pyrogenic in the rabbit at very high dosage levels. Infusion of profibrinolysin in doses equivalent to 100,000 F. U. of activated material in 15 patients did not produce fever.[34]

The role of streptokinase in the febrile reaction remains uncertain. Johnson and coworkers[15] have indicated that the most highly purified preparations of streptokinase avail-

able remain contaminated by antigenic materials that are immunochemically distinct from streptokinase itself. He suggested that these contaminant materials may be responsible for the toxic reactions, including fever, that follow infusions of purified streptokinase. It is possible that pyrogenic residuals that will not activate profibrinolysin are contained in the fibrinolysin preparation used in this study. Proof that such residuals are the source of fever must await the development of either an immunochemically "pure" streptokinase or a nonpyrogenic activator from other sources, such as tissue kinase or urokinase.[4, 11]

The last possibility, that the actions of fibrinolysin prompt temperature elevation, merits consideration. Since many patients fail to develop fever following infusion, it appears unlikely that activation of profibrinolysin renders fibrinolysin pyrogenic per se. However, as has been indicated above, individuals with large thrombotic zones who receive fibrinolysin have significantly higher incidence of temperature elevation than those with small or without thrombotic phenomena. This observation suggests that fibrinolytic attack upon thrombotic material may release breakdown products in such a manner as to provoke pyrogenic reaction. While similar attack of fibrinolysin upon plasma proteins might also be considered, no correlation could be established between fibrinogen or other coagulation factor losses and the incidence or degree of fever. Furthermore, the data indicate that the presence or degree of plasma fibrinolytic activity has no significant relationship to the problem. Johnson and associates[13] have also observed that fibrinolytic activity and pyrogenicity are not parallel phenomena.

At the present time, experimental proof that pyrogenicity arises from products of thrombolysis is lacking. Plasma drawn from patients during and after febrile reactions of fibrinolysin has thus far proved nonpyrogenic in animals. Human recipients of such plasma have not yet been studied.

Since the pyrogenic potential of fibrinolysin presently limits its application in certain critical thrombotic states (e.g., coronary thrombosis), elucidation of its cause is of considerable practical importance. Our recent experience has indicated that fever can be ameliorated or prevented by aspirin-antihistaminic or barbiturate prophylaxis, but reliance upon such measures is obviously less desirable than specific identification and control of those factors involved in the production of fever. That identification of the source of pyrogenicity may involve rather extensive and detailed study, however, has been indicated by several recent investigations regarding pyrogenicity.[35, 36]

The effect of fibrinolysin upon the human coagulative process was one of the focal points of this study. The animal investigations of Cliffton et al.[23, 26] and Ambrus and Back[24, 25] have indicated that a rather wide range of fibrinolysin dosage will produce significant enhancement of plasma fibrinolytic activity without compromise of the coagulation mechanism. In the doses employed in the present study, fibrinolysin infusion in human subjects caused minimal aberration of coagulation factors. While fibrinolysin undoubtedly is subject to the pharmacologic rule of wide individual variation in response, a considerable margin of safety appears to exist in man between dosages that significantly enhance plasma fibrinolytic activity and those that may lead to clinically important impairment of the coagulative process.

The laboratory measurements indicating that no gross disturbance of coagulative process followed fibrinolysin administration correlated well with the clinical observation that no hemorrhagic phenomena occurred in any patient, including 29 simultaneouly receiving coumarin-indandione drugs or heparin. These observations are in agreement with the animal and human experience of Cliffton and Ambrus who noted that bleeding complicated plasma infusion only when excessive doses were given or local vascular lesions existed during periods of high lytic activity.

The ability of fibrinolysin to achieve significant plasma fibrinolytic activity without

adue influence upon coagulation probably effects several independent influences. One factor involved is the capacity of the organism for rapid replacement of depleted components of plasma protein. Absence of depression of a factor cannot be interpreted as absence of destruction in vivo, but it may indicate that restorative mechanisms are able to keep pace with the proteolytic activities of fibrinolysin. The rapidity of fibrinolysin infusion and concentration of the administered solution also may exert a significant influence. While data included here deal with infusions given over 2 hours or more, isolated observations have suggested that rapid infusions of fibrinolysin are accompanied by more profound, though transient, declines in certain factors, especially fibrinogen.

Another circumstance that may limit the degree to which fibrinolysin effects plasma proteins is the apparent *preferential action* of this enzyme upon fibrin.[27] Such preference is probably related not only to the specific protein linkages split by fibrinolysin, but also to the known adsorptive affinity of fibrin for plasma.[4, 11] Such adsorption would tend to concentrate fibrinolysin activity upon intravascular fibrin. In addition, there is in vitro evidence indicating that inhibition or destruction of plasmin occurs more rapidly when suitable substances are not supplied, a chain of events that would also tend to limit the attack of fibrinolysin to fibrin.[37, 38]

Although the dosage of fibrinolysin used in this study produced no major coagulation defects, serious disturbances may arise if higher doses are employed. Back and Ambrus have demonstrated that large dosages of fibrinolysin in the dog may produce significant fibrinogen depression and prothrombin time prolongation.[24, 25] The present studies suggest that any impairment of coagulation induced by fibrinolysin in the human is likely to be reflected first and most obviously by depression of fibrinogen content. Since considerable variability may exist in regard to both the degree of fibrinogenolysis and the fibrinogen-replacement capacities in individual patients, qualitative determination of fibrinogen before and during fibrinolysin administration seems advisable when doses in excess of those used in this study are employed. The same caution regarding higher dosages of fibrinolysin may also apply to the other coagulation factors and to such events as hypotension.

Observations regarding the safety of fibrinolysin infusion in human subjects would have little meaning unless nontoxic doses were also capable of inducing significant intravascular fibrinolytic activity. As indicated above, enhanced fibrinolytic activity is frequently achieved by plasmin even at the lowest dosage levels. Higher doses result in a prolongation and intensification of demonstrable lytic activity, although the intensity of lytic activity is subject to rather wide variation. If one may transpose animal and laboratory data in any degree to man, one might expect frequent success in achieving dissolution of an intravascular fibrin meshwork exposed to the lytic levels achieved by fibrinolysin. However, it is essential to recognize that *no direct evidence exists regarding the degree to which plasma fibrinolytic activity demonstrated in the test tube may be equated with the desired lysis of a human intravascular clot in vivo.* The fragmentary data available suggest that gross correlation can be expected. Indeed, theoretically, the strong adsorptive capacity of fibrin for fibrinolysin should lead to action upon an in vivo clot to a degree and for a duration well beyond that expected on the basis of activity detectable in the circulating plasma.[4] It is probably equally true, however, that achievement of plasma lytic activity does not guarantee dissolution of a susceptible clot. Local factors may prevent adequate access of fibrinolysin to thrombus or result in a variable adsorption of the agent to fibrin. Variations in local inhibitory phenomena may also play a role. Therefore, no firm conclusions can be drawn regarding the therapeutic efficacy of a given degree or duration of plasma lytic activity at this juncture. Dosage of fibrinolysin in various clinical states will re-

main largely empirical until an adequate body of clinical experience has accumulated.

Another facet of the dosage problem is the marked plasma fibrinolytic activity that was achieved by relatively small doses of fibrinolysin. If one estimates blood volume in the patients and calculates the maximum fibrinolysin unitage that might be circulating in the plasma at any given time, it is apparent that 30 F. U./ml. or 12 units/0.4 ml. is the greatest concentration that can be expected. Reference to the standard curve indicates that 12 F. U. in a test system free of plasma inhibitors would give a lysis time of 6 to 7 minutes. Yet, in the assay system with 0.4 ml. of patient's plasma, which should contain considerable inhibitor activity, lysis times of 6 to 7 minutes or below were frequently encountered in 3- and 6-hour samples. This observation suggests that the fibrinolysin preparation prompts more in vivo fibrinolytic activity than can be accounted for in the test tube. Unquestionably, the material used contains components other than fibrinolysin itself. That it does not contain plasminogen activators of the streptokinase type is established during manufacture. But our data suggest that some activator function may occur in vivo through mechanisms that are presently nebulous. As von Kaulla has indicated, materials which are nonfibrinolytic and nonactivator in vitro may assume both these functions in vivo. Further study of the origin of this unexpected fibrinolytic "dividend" is currently being pursued, for the possibility that fibrinolysin may serve as both an activator and a directly fibrinolytic agent in vivo has important clinical implications. Since blood clot itself contains plasminogen, an agent that can simultaneously produce high levels of plasma fibrinolytic activity and activate the plasminogen within the clot should exert a potent thrombolytic effect. Activator materials, such as streptokinase, urokinase, and the bacterial pyrogens, should activate the plasminogen contained in the clot if they are capable of attaching to or penetrating blood clot in vivo, but plasma fibrinolytic activity with these agents would remain dependent upon the availability of plasminogen. Perhaps such effects upon plasimogen within the clot itself might dissolve thrombi more effectively than any level of plasma fibinolytic activity. This possibility requires further exploration. However, if fibrinolysin does contain an activator component, both plasminogen activation within the clot and enhancement of plasma fibrinolytic activity independent of plasminogen levels could be achieved by its administration. Such a combination of effects would appear to represent the broadest therapeutic approach.

A number of other cogent questions require answer before the clinical value of fibrinolysin can be properly assessed. Such questions include the age at which a thrombus becomes resistant to fibrinolysis; the functional return and hemorrhagic hazard that may result in ischemic areas when acute clot dissolution is achieved proximally; the danger of embolism when intravascular clot is acted upon by plasmin; methods for controlling excessive effects of fibrinolysin should they appear; and the need for anticoagulant therapy following acute lysis of thrombi.

At the laboratory level, several problems also warrant further investigation. For instance, the assay procedures for fibrinolytic activity are still a subject of debate. Multiple methods are currently in use, and each has its advantages and disadvantages. In our experience, observation of whole-blood clot lysis following administration of fibrinolytic drugs has been of qualitative value, but it is not subject to quantitation. Spectrophotometric assay with a system containing synthetic acid ester substrates, which are susceptible to the esterase activity of fibrinolysin, are excellent tools for the in vitro measurement of pure fibrinolysin-substrate systems.[39, 40] However, the method appears of less value when used in an attempt to assay the fibrinolytic activity present in plasma. Some 40 patients in this series have had spectrophotometric estimations of plasma esterase activity in parallel with the standard clot assay. Although s-

terase activity showed a qualitative correlation with the clot method, quantitative differences were frequent.

Such enzymatic assays possess several deficiencies. Variable degrees of "nonfibrinolytic" esterase activity may be present in plasma, and its contribution to over-all esterase activity may be difficult to establish. Furthermore, the validity of using a synthetic substrate to replace fibrin in any assay for fibrinolytic activity is subject to question, since the strong affinity of fibrinolysin for fibrin itself may play a significant role in determining the duration and intensity of such activity. Thus, it appears likely that the esterase and fibrinolytic potencies of plasma may not be parallel phenomena. We continue to prefer the fibrinolytic assay described here as the method which yields information of greatest clinical utility.

Despite these challenging clinical and methodologic uncertainties, our observations provide a firm basis for extending investigations with fibrinolysin to the phase of therapeutic trial in patients with thromboembolic disease. They indicate that fibrinolysin, in doses which are tolerated without significant aberration of coagulation processes or other unacceptable consequences, can consistently achieve levels of in vivo fibrinolytic activity that may prove effective in reversing acute thrombotic events. Determination of the ultimate clinical value of this agent in thromoembolic disorders, however, will require extensive and detailed study.

Summary

Seventy-two infusions of human fibrinolysin have been carried out in 63 hospital inpatients to assess the coagulation changes, fibrinolytic activity, and systemic consequences that follow such infusions at various dosage levels.

The effects upon coagulation factors were minor at all dosage levels. Fibrinogen content was depressed more frequently and to a greater extent than any of the other factors measured. No hemorrhagic phenomena were noted in any patient, including 29 who were simultaneously receiving anticoagulant drugs.

Systemic toxicity was limited primarily to a febrile reaction, which occurred in 44 per cent of the total patient group. The source of pyrogenicity remains undefined, but appears related either to nonactivator residuals contained in fibrinolysin or to products released by the action of fibrinolysin upon thrombotic material.

Fibrinolysin infusion consistently enhanced plasma fibrinolytic activity at all dosage levels. The intensity and duration of such enhancement appeared related to fibrinolysin dosage. In some cases, the intensity of fibrinolytic activity achieved in vivo suggested that the material used contained an activator in addition to fibrinolysin per se.

A number of clinical and laboratory questions regarding fibrinolysin must be answered before firm statements can be made regarding the proper application and therapeutic value of this material in human thromboembolic disease.

Summario in Interlingua

Septanta-duo infusiones de fibrinolysina human esseva effectuate in 63 patientes hospitalisate con le objectivo de determinar le alterationes del coagulation, le activitate fibrinolytic, e le consequentias systemic que seque tal infusiones a varie nivellos de dosage.

Le effectos producite in le factores coagulatori esseva de importantia minor a omne nivellos de dosage. Le contento de fibrinogeno esseva deprimite plus frequentemente e plus marcatemente que ulle del altere factores mesurate. Nulle phenomenos hemorrhagic esseva notate in ulle del patientes, incluse le 29 qui se trovava simultaneemente sub tractamento con drogas anticoagulante.

Le toxicitate systemic esseva limitate primarimente a un reaction febril. Isto occurreva in 44 pro cento del gruppo total de patientes. Le origine del pyrogenicitate remane obscur, sed il pare que le phenomeno es relationate al presentia de residuos nonactivatori in le fibrinolysina o a productos que resulta del action de fibrinolysina super le material thrombotic.

Le infusion de fibrinolysina promoveva uniformemente le activitate fibrinolytic in le plasma a omne nivellos de dosage. Le intensitate e le duration de iste effecto esseva apparentemente relationate al dosage de fibrinolysina usate. In plure casos, le intensitate del activitate fibrinolytic attingite in vivo suggereva que le material usate contineva un activator a parte le fibrinolysina per se.

Un numero de questiones clinic e laboratorial con respecto al natura de fibrinolysina debe esser resolvite ante que firme assertiones deveni possibile con respecto al uso appropriate e al valor therapeutic de iste substantia in casos de morbo thrombo-embolic in humanos.

ACKNOWLEDGMENT

The author wishes to thank Mrs. M. B. Jefferson and Mrs. J. B. Burbank, medical technicians, without whose devoted efforts the study could not have been accomplished; the technical staff of the biochemistry division of the Ortho Research Foundation for their close cooperation; Dr. Louis Nanni, of Rutgers University, for statistical analysis of the experimental data; and the medical and nursing staffs of the District of Columbia General Hospital, for their support and assistance in all phases of this investigation.

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There is now a danger, of which Professor Laubry warned us in Paris, that Cardiology will become no more than the application of laboratory techniques to patients, and so will cease to belong to Clinical Medicine. It is unlikely that technical procedures, however perfected, can ever become a substitute for diligent clinical observation and therefore it behooves us to pass on to the next generation the clinical skill and wisdom which we have inherited from our teachers of the past.—Evan Bedford. *Address of the President of the European Society of Cardiology.* IIIrd World Congress of Cardiology, Brussels, September 14-21, 1958, p. 29.

Effect of Anticoagulants on Experimental Cerebral Infarction

Clinical Implications

By JACK P. WHISNANT, M.D., M.S., CLARK H. MILLIKAN, M.D., GEORGE P. SAYRE, M.D., M.S., AND KHALIL G. WAKIM, M.D., PH.D.

Cerebral infarction is attended by extravasation of blood in varying degrees. The present study was undertaken to learn whether anticoagulant therapy increases the extravasation and thereby diminishes or negates possibly favorable therapeutic effects. A series of experiments on dogs is described and the clinical implications are discussed.

THE use of anticoagulant therapy in cerebrovascular disease has become a widely, though not universally, accepted practice. There are specific categories of cerebrovascular disease in which anticoagulant therapy has seemed definitely beneficial.[1] Clinical interest in this field led us to carry out a series of experiments to obtain evidence in regard to the effect of anticoagulant therapy on completed cerebral infarction in dogs. Blumgart and associates[2] have studied the effects of bishydroxycoumarin (Dicumarol) immediately after myocardial infarction in dogs. A comparison of the results with those in a control group did not show a difference in the hemorrhagic extravasations in the infarcts nor in the size of the infarcts. The difference in the structure of the brain as compared to the heart warrants further investigation in regard to the effects of anticoagulants on cerebral infarction. This report is a compendium in which we have brought together our accumulated experience on this subject.[3-6] We shall indicate that there is, indeed, an increased risk in administering anticoagulants under the conditions of these experiments, and shall emphasize its clinical implications.

METHODS

Two methods have been used for the production of experimental cerebral infarction in dogs. With either method infarction has developed in 70 to 80 per cent of the animals. The first method was the introduction, into one internal carotid artery in the neck, of approximately 0.2 ml. of liquid vinyl acetate* through a 20-gage needle. This material polymerized or hardened when it came in contact with the blood and formed a more or less continuous strand of solid material in the internal carotid and middle cerebral arteries and sometimes extended into the anterior cerebral and posterior communicating arteries. Therefore, it did not represent an embolus in the usual sense, but it did occlude a relatively long segment of the vascular tree to the brain on one side. It was rarely found in the opposite side of the circle of Willis.

The second method was the introduction, through a 20-gage needle, of 0.2 ml. of 48-hour-old autologous clot into 1 internal carotid artery in the neck. Venous blood was obtained 2 days prior to the operative procedure and allowed to clot at room temperature in a sterile tube. We found that 48 hours was the optimal time to use the clotted blood for this purpose. The clot was blotted dry and small fragments of it were placed in a 1-ml. syringe to a total amount of 0.2 ml. When the material was introduced into the internal carotid artery through a 20-gage needle, the clot fragments stopped in various places, especially at bifurcations of the cerebral arteries. This, therefore, represented the injection of multiple clot emboli into one internal carotid artery. Rarely did these embolic fragments go into arteries on the opposite side of the circle of Willis.

RESULTS

Examination of the brains at necropsy revealed the infarcts, with or without anticoagulants, to be partly pale and partly hemorrhagic. In order to record the extent of an

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

*Vinyl acetate for this study was obtained from Ward's Natural Science Establishment, Rochester, N. Y.

infarct and the extent of hemorrhagic infarction for comparison, we cut each brain into 7 standard coronal slices. A scale drawing was made representing each coronal slice and these were reproduced on printed forms so that each infarct could be depicted in its total extent and its extent of hemorrhagic infarction. These areas were then traced with a planimeter to measure the total areas involved on the 7 coronal slices, and from these figures the percentage of hemorrhage in an infarct was computed. The limitations of such a scheme are obvious, but it has proved useful to compare various infarcts by numerical figures rather than by visual impressions.

Practically all of the infarcts produced by vinyl acetate were less than 30 per cent hemorrhagic (table 1). One extremely hemorrhagic lesion in this group was an exception to the relatively pale infarcts produced by this method. Our earlier experience with 37 infarcts produced by injection of vinyl acetate gave further evidence that infarcts produced by this method are relatively nonhemorrhagic.

On the other hand, the infarcts that were produced by injection of autologous blood-clot fragments varied in their hemorrhagic extent, but it was found that two thirds of those that were less than 12 days old were more than 60 per cent hemorrhagic. This would seem to support the contention that embolic infarcts are usually rather hemorrhagic. There were notable exceptions to this finding; in the group studied 2 infarcts were rather pale and 4 had only a mild to moderate hemorrhagic character (table 1).

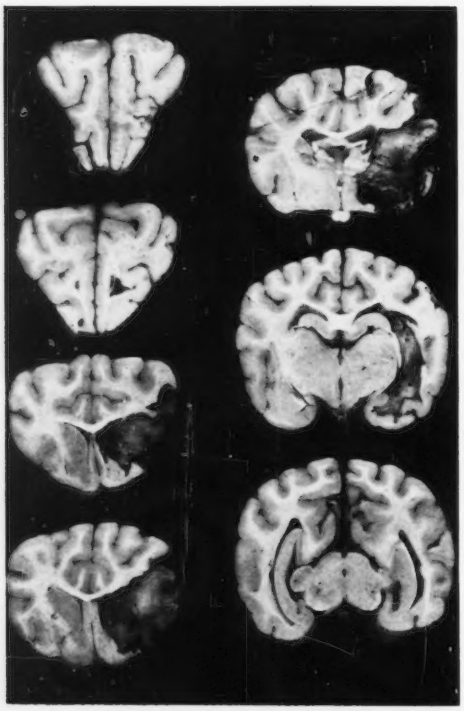
When ethyl biscoumacetate (Tromexan) and bishydroxycoumarin (Dicumarol) were given orally to dogs, approximately 24 hours was required to reduce the prothrombin activity to a therapeutic range (10 to 30 per cent). We found that an initial oral dose of 30 to 40 mg. of Tromexan and 10 to 25 mg. of Dicumarol, depending on the weight of the animal, was adequate to attain the therapeutic range in 24 hours. Thereafter it required from 0 to 10 mg. of Dicumarol daily for

TABLE 1.—*Extent of Hemorrhagic Infarction in Seven Coronal Brain Slices: Infarcts Produced by Vinyl Acetate and by Clot Fragments*

Hemorrhagic area in infarct, (%)	Occluding material			
	Vinyl acetate		Autologous clots	
	Number of infarcts	Per cent	Number of infarcts	Per cent
0 to 30	13	93	2	11
31 to 60	0	0	4	22
61 to 90	0	0	4	22
91 to 100	1	7	8	45

maintenance, depending on the prothrombin time. The prothrombin times were determined by the Quick method as modified by Hurn, Barker, and Magath[7] with use of Difco thromboplastin. The control prothrombin times ranged from 6 to 8 seconds in all animals. In the studies mentioned herein the prothrombin activity is noted in percentage of normal, which was established from a curve made by determining the prothrombin time of serial dilutions of plasma with saline. For example, a prothrombin activity of 20 per cent is equivalent to the prothrombin time obtained with a 20 per cent concentration of normal dog plasma.

Our initial experience in administering anticoagulants to dogs with cerebral infarcts involved 13 animals that were given Tromexan and Dicumarol on the same day the infarcts were produced. The infarcts were produced by intracarotid injection of vinyl acetate, which, as noted previously, caused relatively pale or nonhemorrhagic infarcts. In this group, the prothrombin activity was intentionally maintained excessively low by giving an excessive amount of anticoagulant. The average of the lowest values for each animal was 5 per cent prothrombin activity. Eleven of these infarcts were strikingly hemorrhagic when compared with the relatively pale infarcts in the 13 control dogs. Animals survived at least 30 hours to be included in either group. A considerable range of degree of hemorrhage was noted, often in the same infarct (fig. 1, top). In 5 animals the entire infarct was occupied by hemorrhage, and in 1



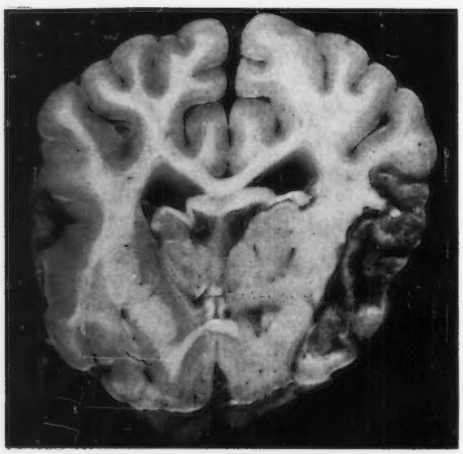


FIG. 1. *Top.* Infarct produced with injection of vinyl acetate. Anticoagulants started same day and continued for 12 days, when dog was killed. Margins of infarct are more densely hemorrhagic than remainder of infarct. *Bottom.* Infarct produced with injection of vinyl acetate. Animal received anticoagulants full period of study (12 days). Completely pale infarct.

TABLE 2.—*Effect of Anticoagulants on Extent of Hemorrhage in Cerebral Infarcts Produced by Vinyl Acetate*

Hemorrhagic area in infarct, (%)	Group of dogs			
	Control		Given anticoagulants	
	Number	Per cent	Number	Per cent
0 to 30	13	93	16	64
31 to 60	0	0	8	32
61 to 90	0	0	1	4
91 to 100	1	7	0	0

of these intraventricular hemorrhage was noted.

It was rather obvious that the infarcts were considerably more hemorrhagic in the animals with excessively reduced prothrombin activity than in the controls. We then conducted a similar study, making sure that the prothrombin activities were maintained within a reasonable therapeutic range (10 to 30 per cent).[4] For 2 reasons this study was limited to animals that survived at least 48 hours: (1) so that full anticoagulant activity could be effected, and (2) because most control animals as a result of the infarct died within 48 hours. Therefore the period of high mortality from the infarcts alone was eliminated from this part of the study.

The hemorrhagic zones in these infarcts were mapped on the printed representations of the standard brain slices and were compared to similar regions in a group of 14 control animals (table 2). It was apparent that the infarcts in the group that received anticoagulants were significantly more hemorrhagic than those in the control group. However, 1 cortical infarct in the control group was almost entirely hemorrhagic, though not densely so, and infarcts in 2 dogs that received anticoagulants had no hemorrhagic character (fig. 1, bottom). All control animals in this group that lived for 3 days after an infarct was produced survived until termination of the study at 12 days. To the contrary, in the group that received anticoagulants and survived at least 3 days, 8 of 20 animals (40 per cent) died prior to the termination of the study. The conclusion is that the administration of anticoagulants to these animals in-

creased the hemorrhagic character of their cerebral infarcts and also increased the hazard of death for the animals.

As for the infarcts produced by emboli consisting of autologous blood-clot fragments, it should be kept in mind that these infarcts were ordinarily rather hemorrhagic even without influence from other agents. Twenty dogs received Tromexan and Dicumarol for 48 hours prior to the intracarotid injection of the clot fragments, so that a therapeutic range of reduced prothrombin activity existed at the time the infarct was produced. After the infarcts were produced, the prothrombin activity was maintained close to the therapeutic range (10 to 30 per cent) by oral administration of Dicumarol. The hemorrhagic character of the infarcts was compared with that of the infarcts of 18 control animals in which the infarcts were produced in the same manner, but no anticoagulant was given. The animals receiving anticoagulants were matched with the control group as to the age of the infarcts, which ranged from 8 hours to 12 days.

A wide range in the extent of hemorrhagic character of the infarcts was noted in each group of this study. The percentage of the infarct which was hemorrhagic in the mildly and moderately hemorrhagic infarcts corresponded almost exactly in the control group and the group which received anticoagulants (0 to 90 per cent hemorrhagic). However, 8 of 18 animals in the control series and 12 of 20 in the group which received anticoagulants had infarcts that were more than 90 per cent hemorrhagic (table 3; fig. 2). While these latter figures are suggestive of an adverse effect from the anticoagulants, the differences are not statistically significant in a series of this size. This suggestive adverse effect is perhaps increased by the fact that frank hemorrhage occurred within 2 infarcts in dogs which received anticoagulants, and in 1 of these intraventricular hemorrhage was present. The prothrombin activity in the latter dog was inadvertently reduced to 5 per cent. Frank hemorrhage was not noted in any of the infarcts in the control animals.

TABLE 3.—*Effect of Preinfarction Anticoagulants on Extent of Hemorrhage in Cerebral Infarcts Produced by Clot Fragments*

Hemorrhagic area in infarct, (%)	Group of dogs			
	Control		Preinfarction anticoagulants	
	Number	Per cent	Number	Per cent
0 to 30	2	11	2	10
31 to 60	4	22	2	10
61 to 90	4	22	4	20
91 to 100	8	45	12	60

To get a more comprehensive picture of the effect of anticoagulants on experimental cerebral infarction, we used another group of animals in which we delayed the administration of Tromexan and Dicumarol for 3 days after the infarcts were produced. For this study 48-hour-old autologous clot fragments were injected to produce the infarcts. The therapeutic range of reduced prothrombin activity was achieved within 24 hours; thus the full effect of the anticoagulants first occurred 4 days after the infarcts were produced. A prerequisite for this study was that a dog with an infarct had to survive at least 3 days to be included in either the control group or the group given anticoagulants. Only those dogs with clinically detectable infarcts were used, and thus each animal had hemiparesis or forced circling or both. The incidence of cerebral infarction by these criteria was 70 per cent. A number of dogs died in the first 3 days, usually within 48 hours, and were not used in this part of the study.

Twenty-three dogs were used as controls; 14 were killed when the cerebral infarct was 12 days old and 9 were killed when the infarct was 18 days old. Twenty-eight dogs were started on anticoagulants after 3 days, but 4 of these died before the study ended. One died on the eighth postoperative day as the result of intracerebral hematoma and intraventricular hemorrhage. In 2 animals death resulted from gastrointestinal bleeding on the seventh and ninth postoperative days respectively. Paradoxically, even with the severe gastrointestinal bleeding and rather large

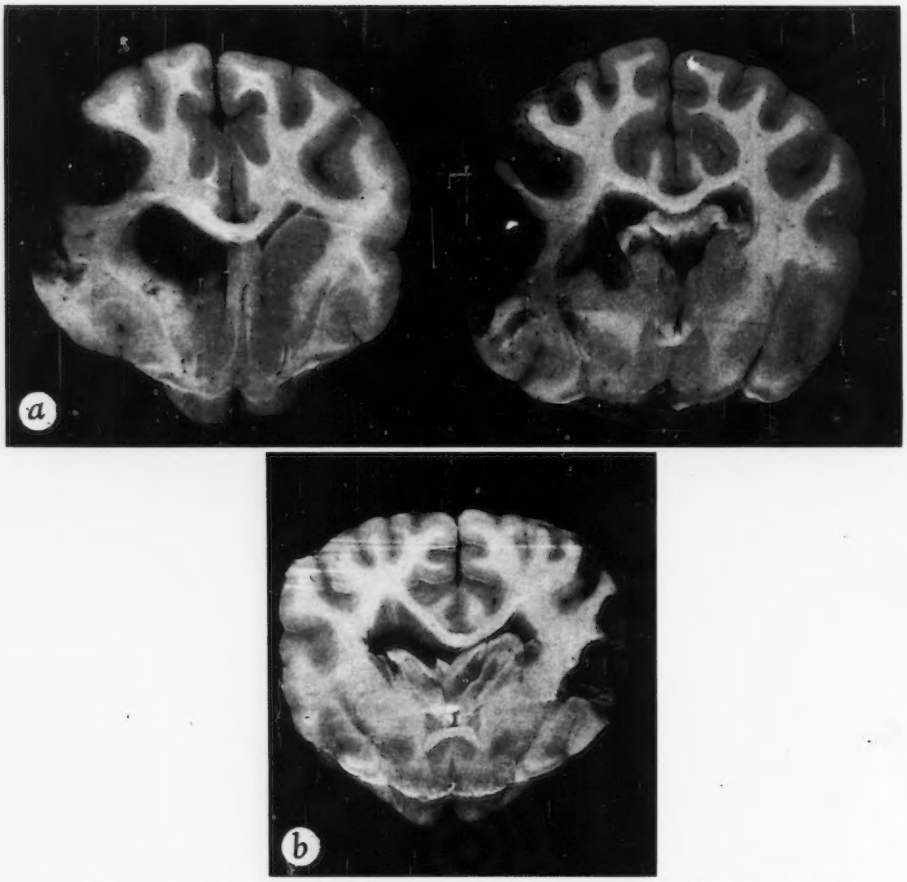


FIG. 2. *a*. Control hemorrhagic infarct produced by clot fragments. *b*. Infarct produced by clot fragments. Animal received anticoagulants starting 2 days before infarct was produced.

cerebral infarcts, these infarcts were only minimally hemorrhagic, one being 14 per cent and the other 4 per cent hemorrhagic. In all 3 animals which died, the prothrombin activity had dropped to less than 5 per cent sometime during the period of observation. The fourth animal died of meningitis on the fifth postoperative day. Of the other 24 animals given anticoagulants, 15 animals were treated for 9 days, making the infarcts 12 days old, and 9 animals were treated for 15 days, making the infarcts 18 days old, when the animals were killed.

Most infarcts in the control animals were only mildly hemorrhagic. However, 17 per cent of the dogs which received anticoagulants had infarcts that were more than 60 per cent hemorrhagic, while none of the infarcts in the control group was more than 60 per cent hemorrhagic. Stated in another way then, 4 of the dogs given anticoagulants had infarcts which were more hemorrhagic than the most hemorrhagic infarct of the control group (table 4). Besides the 1 dog already noted which died as the result of an intracerebral hematoma, there were 2 other dogs in the group given anticoagulants which had gross hematomas in their cerebral infarcts and survived (fig. 3, top). The prothrombin activity in both of these dogs was less than 5

TABLE 4.—*Effect of Delayed Administration of nticoagulants on Extent of Hemorrhage in Cerebral nfarcts Produced by Clot Fragments*

Hemorrhagic area in infarct, (%)	Group of dogs			
	Control		Delayed anticoagulants*	
	Number	Per cent	Number	Per cent
0 to 30	20	87	16	67
31 to 60	3	13	4	17
61 to 90	0	0	3	13
91 to 100	0	0	1	4

*This table excludes 4 animals that received anti-oagulants and died during the observation period.

per cent. No hematomas were noted in the control animals. In all of our studies of anticoagulants, regardless of how low the prothrombin activity was reduced, we did not see hemorrhage in the brain of an animal except when it was within an infarct or had ruptured from such an infarct into the ventricles.

It may be noted that in this study neither the control animals nor the animals given anticoagulants had infarcts which were as hemorrhagic as even the control animals in the previously cited study with infarcts from clot fragments (table 3). This is apparently because of the age of the infarcts, since in the earlier study (table 3) the ages of the infarcts averaged 1 week, while in this study (table 4) the average age of the infarcts was more than 2 weeks. Apparently this difference in time is adequate for absorption of part of the hemorrhagic element of the infarcts, in spite of continued administration of the anticoagulant.

In order to estimate whether the animals which received anticoagulants derived any protection from them in terms of the total areas of infarction, the areas were determined from the 7 coronal brain slices of these animals for comparison with similar slices from control groups. In the group of dogs which received Tromexan and Dicumarol 48 hours prior to intracarotid injection of clot fragments, the prothrombin activity was in therapeutic range at the time of the injection. In these animals the comparison was limited to those infarcts more than 24 hours old, so that

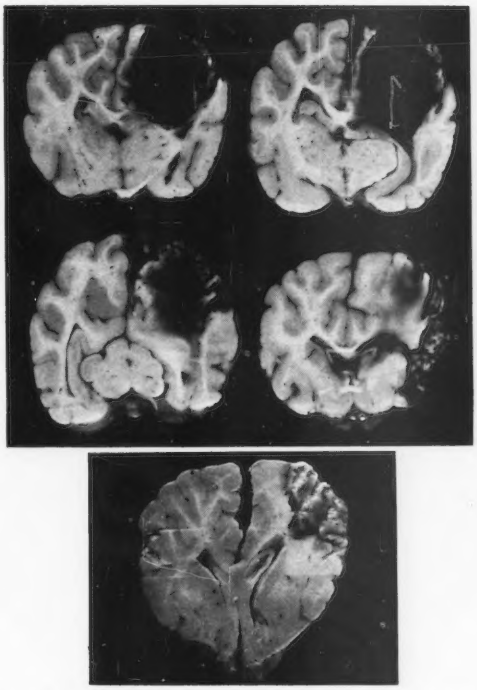


FIG. 3. *Top.* Infarct produced by injection of clot fragment. Anticoagulants started 3 days after infarct was produced. Note large hematoma. Dog did well and survived full period of study. *Bottom.* Infarct produced by injection of clot fragment. Dog died on ninth postoperative day from massive gastrointestinal bleeding. Cerebral infarct is pale.

they would be well demarcated. A larger percentage of animals given anticoagulants had small infarcts when compared with the control group. Five of the 18 control animals had infarcts which were larger than the largest infarct in the group given anticoagulants (table 5). The largest infarct in the control group had 2317 mm.^{2} of infarction in the 7 brain slices, while the largest infarct in the group given anticoagulants had 1051 mm.^{2}

Thus it would appear that the anticoagulants offered some protection, and one could surmise that some of the clot fragments which might have caused infarction could have proceeded to smaller branches and caused less damage in the animals which received anticoagulants. However, some cerebral infarc-

TABLE 5.—*Effect of Preinfarction Anticoagulants on Size of Cerebral Infarcts Produced by Clot Fragments*

Size of infarct in seven coronal brain slices (mm.²)	Group of dogs	
	Control (20)	Given anticoagulants (20)
0 to 300	8	13
301 to 600	3	5
601 to 1100	4	2
1101 to 1600	2	0
More than 1600	3	0

TABLE 6.—*Effect of Anticoagulants Given Three Days after infarction on Size of Cerebral Infarcts Produced by Clot Fragments*

Size of infarct in seven coronal brain slices (mm.²)	Group of dogs	
	Control (23)	Given anticoagulants (24)
0 to 200	9	10
201 to 500	8	5
501 to 1000	4	4
1001 to 1500	1	2
More than 1500	1	3

tion developed in approximately 70 per cent of the animals which received anticoagulants, and this is in accord with the 80 per cent incidence of infarction in the control group.

When the administration of anticoagulants was delayed for 3 days after the infarcts were produced, the size of infarcts did not differ significantly from that of infarcts in the control group (table 6). In this instance, of course, the infarcts were completed before anticoagulants were started. Therefore, even though the extent of hemorrhagic element was somewhat greater in the infarcts of this group of dogs which received anticoagulants, the hemorrhagic component did not cause any statistically detectable extension of the damaged region.

The dogs that received anticoagulants prior to infarction were operated on while they had significantly reduced prothrombin activities. The operations were performed on the neck to expose the region of the common carotid bifurcation and the nearby branches. This required a moderate amount of dissection. When the prothrombin time was 15 seconds or less, with a control time of 6 to 7 seconds, slight if any difficulty was experienced in controlling bleeding at the time of operation. In this study a prothrombin time of 15 seconds represents approximately 16 per cent prothrombin activity. When the prothrombin time was longer than 15 seconds there was a problem of varying degree with hemostasis. It was never insurmountable at the time of the procedure, but, for example, it was occasionally necessary to apply firm pressure for 5 to 10 minutes on the hole made in the artery by the 20-gage needle to prevent bleeding after injection of the occluding material.

Another feature of the preoperative anticoagulant therapy, however, is the occurrence of local hemorrhagic complications after treatment and during the period of observation. Twenty-nine animals were operated on while under effective anticoagulant therapy and 9 of these had some form of hemorrhagic complication at or near the operative site. Four animals had moderate bleeding in the neck at the operative site; 1 animal had a large hematoma in the same region; and 4 animals had large hematomas in the neck with extension into the mediastinum. None of these animals had excessively prolonged prothrombin times during the period of observation. Even when a hematoma was present, the skin wound usually healed satisfactorily. When there was no hematoma, the neck wounds healed promptly.

In our search for occluded cerebral arteries after intracarotid injection of the clot fragments, we made a study chiefly of the major cerebral arteries. In both the animals that received and did not receive anticoagulants some of the occlusions were caused only by the 48-hour-old autologous clot fragments that were injected. Under microscopic examination of tissue stained with hematoxylin and eosin, rather homogeneous material was found that stained pale pink and partly or completely filled the involved artery. Usually little reaction was evident between this material and the vessel wall. The material consisted of poorly stained erythrocytes, strands of fibrin and

disintegrating leukocytes. Other occlusions were caused by an organizing thrombus attached to the vessel wall with or without the adjacent palestaining homogeneous material just mentioned.

Occluded cerebral arteries were found in approximately 80 per cent of all animals with infarction which did not receive anticoagulants (97 dogs). When the administration of anticoagulants was delayed for 3 days, the percentage of occluded arteries was approximately the same (83 per cent). When the anticoagulants had been given 2 days before cerebral infarction, occlusions were found in only 45 per cent of the animals. It is interesting, however, that even with the prothrombin activity reduced to 10 to 30 per cent at the time of the clot-fragment injection, there was still a significant percentage of animals in which the major cerebral arteries were occluded.

Discussion

There is no doubt that under the conditions of these studies, anticoagulants caused an increase in the amount of hemorrhage noted in cerebral infarcts of dogs, regardless of whether the infarcts were produced with injection of vinyl acetate or with autologous blood-clot fragments. This adverse hemorrhagic effect was less apparent in the infarcts produced with clot-fragment emboli, since these infarcts were relatively hemorrhagic even without the administration of anticoagulants. Sibley and associates[8] also concluded that the administration of Dicumarol increased the hemorrhagic component of canine cerebral infarcts produced by embolic clot fragments.

Since the experimental evidence presented here is unfavorable in regard to anticoagulants given for completed infarction, it is necessary to differentiate this situation from the clinical conditions in which anticoagulants are now used. The current indications for anticoagulant therapy in cerebrovascular disease have recently been pointed out[1]: (1) intermittent insufficiency in the vertebral-basilar circulation, (2) intermittent insufficiency in the carotid system, (3) thrombosis in the vertebral-basilar system with infarction, and (4) actively advancing occlusion of the carotid system. The adverse hemorrhagic infarction we have noted in dogs should not in any respect preclude the use of anticoagulants in the first 3 categories mentioned. The first 2 indications deal entirely with prevention of infarction and the third indication, basilar thrombosis, deals primarily with frequently fatal infarction in the brain stem, which, in our experience, is less likely to be hemorrhagic. Anticoagulant therapy also has decreased the mortality figures so much for basilar thrombosis, that any presumed risk from anticoagulants appears justified. The fourth indication also is primarily prevention, that is, prevention of complete infarction from progressive thrombosis. In such instances the cerebral infarction already present is small or at least incomplete. However, in this category there is reason to draw clear lines in regard to accuracy of diagnosis, before the administration of anticoagulants.

We have accepted as valid a fifth indication for use of anticoagulants, that is, multiple thromboembolic episodes, because of the evidence presented by McDevitt and associates.[9] Our own experience in this category has been only fragmentary. Again, increased hemorrhage in the experimental canine cerebral infarcts should not militate against the use of anticoagulants in this category, since the favorable evidence that has been presented is in regard to prevention of anticipated thromboembolic episodes. Our experiments would point out some potentially unfavorable possibilities, if the anticoagulants were started within 3 days of a previous cerebral infarct.

In our experimental setup, there are differences from the potential clinical situations which should be pointed out. In the first place, with the 48-hour autologous clot, we have injected multiple emboli, frequently resulting in multiple or massive infarcts. This is in contrast to the usual single embolus producing a variable cortical hemorrhagic infarct in the closest comparable clinical situation.

Second, these experimental infarcts often encroached on the ventricular system, since they were often large in comparison to the total volume of brain. This made rupture into the ventricle more likely, whatever the instigating factor. Third, as we have demonstrated previously,[10] dogs have an extremely generous collateral circulation to the brain in contrast to human beings. It is not easy to say whether this advantage in collateral circulation is beneficial or whether it may be harmful, in regard to hemorrhage within an infarct, when anticoagulants are added to the picture. Meyer[11] has demonstrated experimentally that when heparin and Dicumarol are administered, the properties of the blood are such that it flows with less resistance in these small collateral channels. Thus more available collateral channels after occlusion conceivably could allow more access of blood to the region of the infarct. The last difference to be noted is that the cerebral arteries of the experimental animals were without atherosclerotic change. While this is in contrast to much of the clinical material with cerebrovascular disease, it is comparable to many clinical situations in regard to cerebral emboli.

The crux of this matter is a problem not directly related to any of the clinical indications for anticoagulants previously cited: that is, whether anticoagulants are helpful or harmful or neither in the immediate treatment of cerebral infarction. The experimental evidence we have presented herein points out that in this situation in dogs, anticoagulants are harmful. Clinical impressions from a limited number of cases would lead us to conclude that anticoagulant therapy in recently completed cerebral infarction does not favorably influence the natural history of the condition. However, neither have we been impressed by the amount of hemorrhage in the cerebral infarcts in such patients who have died as a result of their infarction. Recently, Carter[12] has shown in a limited series that there was a statistical advantage in the use of anticoagulant therapy immediately after cerebral infarction from embolism. This advantage was in regard both to extent of recovery and survival. Also he noted that there was not unusual and extensive hemorrhage in the cerebral infarcts of the 7 patients who failed to survive after such anticoagulant therapy.

When we examine our evidence in regard to all the cerebral infarcts from the clot fragments, we find additional data. Of all such animals which survived longer than 2 days, that is, with exclusion of the period of high mortality from the infarct alone, there were 37 control dogs; there were also 37 dogs which received anticoagulants either before or after the infarction. All of the control animals survived the full period of observation. There were 4 deaths in the group which received anticoagulants. Two of these deaths were associated with gross intracerebral and intraventricular hemorrhage, and 2 deaths were related to massive gastrointestinal bleeding. In neither of the latter 2 dogs was there unusual bleeding in cerebral infarcts, even though infarcts were large (fig. 3, bottom). In all 4 dogs which died, the prothrombin activity had dropped to less than 5 per cent, that is, the dogs had received excessive anticoagulant therapy.

Our experimental evidence presents the antagonist's point of view in regard to the use of anticoagulants immediately after completed cerebral infarction. However, we do not consider that the evidence precludes the desirability of further clinical investigation of potential benefit from properly administered anticoagulant therapy in recently completed cerebral infarction, particularly infarction from embolism.

Summary

Cerebral infarction has been produced by intracarotid injection of either liquid vinyl acetate or 48-hour-old autologous clot fragments. With either method, the administration of anticoagulants increased the hemorrhagic component of the infarcts. This increase was less apparent in the infarcts produced by clot fragments since these are relatively hemorrhagic infarcts even without anticoagulants. Preinfarction anticoagulants

appeared to give some protection in terms of total amount of cerebral infarction after injecting clot fragments. Postinfarction anticoagulants did not give this protection. The evidence cited here regarding increased hemorrhage in completed cerebral infarcts with anticoagulant therapy does not necessarily militate against the use of this treatment in certain well-defined categories of cerebrovascular disease.

Summario in Interlingua

Infarcimento cerebral esseva producite per le injection intracarotidic de (1) liquide acetato vinylic o (2) autologe fragmentos de coagulo de un etate de 48 horas. In ambe casos, le administration de anticoagulantes augmentava le componente hemorrhagic del infarcimentos. Iste augmento esseva minus apparente in le caso del infarcimentos producite per fragmentos de coagulo, proque istos es relativemente hemorrhagic mesmo sin anticoagulantes. Le administration de anticoagulantes ante le production del infarcimentos pareva provider un certe grado de protection, a judicar per le amonta total de infarcimento cerebral trovate post le injection de fragmentos de coagulo. Anticoagulantes administrate post le production del infarcimentos non provideva un tal protection. Le hic-reportate observationes con respecto a augmentos de hemorrhagia in completate infarcimentos cerebral resultante de therapia anticoagulante non representa necessarimente un argumento contra le uso de iste tractamento in certe ben-definite categorias de morbo cerebro-vascular.

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Effect of Oxygen on Pulmonary Vascular Resistance in Patients with Pulmonary Hypertension Associated with Atrial Septal Defect

By H. J. C. Swan, M.B., M.R.C.P., Ph.D., Howard B. Burchell, M.D., Ph.D., and Earl H. Wood, M.D., Ph.D.

The present studies are concerned with the effect of high oxygen inhalation on patients with atrial septal defects. The problem of the amount of pulmonary vascular resistance and the relative contribution of irreversible structural changes and vascular tone may be of important prognostic significance in evaluation of such patients for cardiac surgery.

LOWERED concentrations of oxygen in the inspired air have been shown to produce constriction of pulmonary vessels in the cat[1, 2] and in human subjects.[3, 4] The reaction of canine pulmonary vessels to hypoxia has been studied by many workers, whose consensus appears to favor a constrictor response. However, its variability has caused Lanari-Zubiaur and Hamilton[5] to question its biologic significance. Conversely, concentrations of oxygen approaching 100 per cent in inspired air have been shown to reduce total pulmonary resistance in normal man[6] and in patients with ventricular septal defect[7] and in patients with patent ductus arteriosus.[8]

The present report concerns patients with pulmonary hypertension associated with atrial septal defect, who, in general, fall in an older age group than do patients with ventricular septal defect and who may differ from them in the factors underlying the development of pulmonary hypertension. It will be shown that in these patients with pulmonary hypertension and atrial septal defect, a labile component of the pulmonary vascular resistance can usually be demonstrated whether or not the vascular resistance is increased. Breathing high concentrations of oxygen usually produces a decrease in the calculated pressure-flow ratio (vasomotor tone) even in older patients and in those with severe organic occlusive changes in the pulmonary blood vessels.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

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Material and Methods

Forty patients with atrial septal defect in whom the pulmonary-artery systolic pressure exceeded 60 mm. of mercury were studied by cardiac catheterization at the Mayo Clinic between January 1, 1955, and December 31, 1957. In 30 of these, pulmonary blood flows were determined while they were breathing air and also while they were breathing concentrations of oxygen that approached 100 per cent. Seventeen of the 30 patients underwent surgical correction of their defect, at which time the diagnosis was confirmed. An eighteenth patient was studied following an unsuccessful attempt at operative closure elsewhere. Of the other 12, 6 were rejected as candidates for corrective operation on the basis of severe pulmonary hypertension, systemic blood flow significantly exceeding pulmonary blood flow in all 6. A variety of reasons kept the remaining 6 patients from undergoing operation.

The age of 1 patient was less than 20 years; 7, 9, and 10 patients were in the third, fourth, and fifth decades of life, respectively; and 3 patients were more than 50 years of age.

Seventeen of the patients breathed 95 to 100 per cent oxygen via a mouthpiece with wide-bore corrugated rubber tubing from a large-volume (approximately 45 L.) spirometer, which incorporated a recirculation pump and carbon dioxide absorber and permitted the measurement of oxygen consumption. Thirteen patients breathed oxygen from a molded rubber mask strapped to the face, which incorporated a small balloon and into which oxygen flowed at a rate sufficient to produce a large outboard leak. In this way any tendency for air to be drawn into the face-piece was minimized, and appreciable rebreathing was prevented. This technic, however, did not permit the measurement of oxygen consumption.

Pulmonary blood flow was determined by the Fick principle. Oxygen consumption was determined for all patients while breathing air by measuring the volume of gas expired over a 3-minute interval and determining the oxygen concentration in a sample of this expired gas by the Haldane

ethod. Midway during the collection of expired ir for determinations of oxygen consumption, lood samples were drawn simultaneously from the ulmonary artery and the radial artery. In all ases records of pulmonary artery and systemic rtery pressures were obtained by means of strain- age manometers at this time. The right atrial ressure was measured from a record obtained arlier in the procedure.

The oxygen breathing was started, and after a inimal interval of 5½ minutes (average interval or the group: 7 minutes) additional blood sam- les were withdrawn from the pulmonary and adial arteries. Oxygen consumption was meas- ured in the 17 patients who breathed oxygen from the spirometer, and was assumed to have remained unchanged during oxygen breathing in the others. Recordings of pressure were obtained during the period of collection of blood samples while the patient was breathing 100 per cent oxygen. The catheter then was withdrawn to the right atrium, where a further pressure record was obtained.

Blood samples were analyzed manometrically for oxygen content by the method of Van Slyke and Neill,[9] and the hemoglobin capacity for oxy- gen was determined by the method of Sendroy[10] as modified by Roughton and associates.[11] Pul- monary blood flow (Q_p, L./min.) was calculated according to the formula:

$$Q_p = \frac{O_2}{(C_{pv} - C_{pa})},$$

in which O_2 is the oxygen consumption in milli- liters per minute and the C's with subscripts indi- cate the oxygen content of pulmonary vein and pulmonary artery bloods, respectively, in milli- liters per liter. In 21 of the 30 cases the arterial oxygen saturation was less than 94 per cent when he patients breathed air. One patient from whom clear history of postoperative pulmonary em- olism was elicited was found to have a pulmonary in oxygen saturation of 93 per cent; but in 6 her patients, 4 of whom had significant desatura- n of systemic artery blood, the saturation of ulmonary vein blood ranged from 97 to 99 per nt. Accordingly, when these values were not asured, the assumption was made that the hemo- bin saturation of pulmonary venous blood was per cent when the patient breathed air and per cent when the patient breathed 99 to per cent oxygen, and that 0.3 and 1.8 volumes oxygen per 100 ml. of blood were present in d solved form under the two circumstances. These d ived values were used in the determination of Q_p.

he ratios of pressure to flow referred to as to l pulmonary and pulmonary vascular resist- ances R_p and R_{pv}, in dynes sec. cm.$^{-5}$) were de- termined according to the formulae:

$$R_p = \frac{\bar{P}_{pa} \times 1332 \times 60}{Q_p} \text{ and}$$

$$R_{pv} = \frac{(\bar{P}_{pa} - \bar{P}_{la}) \times 1332 \times 60}{Q_p},$$

in which the terms $\bar{P}_{pa}$ and $\bar{P}_{la}$ represent the mean pulmonary artery and mean left atrial pressures (mm. Hg), the mean left atrial pressure being as- sumed to equal mean right atrial pressure.

Results

The oxygen consumption measured in all 30 patients while breathing air averaged 145 ml. per min. per M.^{2} Among the 17 in whom it was measured while they were breathing 95 to 100 per cent oxygen, it averaged 143 ml. per min. per M.^{2} during breathing of air and 148 ml. per min. per M.^{2} during breathing of oxygen.

During the period of breathing air and breathing 100 per cent oxygen, respectively, the average pressures in the pulmonary cir- cuits were 90 and 81 mm. Hg systolic, 37 and 34 diastolic, and 55 and 50 mean. The mean pulmonary artery pressure declined in 26 cases, was unchanged in 3, and increased in only 1 (fig. 1). This response apparently was not related to the initial levels of pressure. Pulmonary blood flow averaged 4.5 L. per min. per M.^{2} while breathing air and 5.5 L. per min. per M.^{2} while breathing oxygen (fig. 1). Generally, larger changes in pressure were associated with larger changes in blood flow (fig. 2). Thus the total pulmonary resistance, which averaged 712 dynes sec. cm.$^{-5}$ while breathing air, declined to an average of 550 dynes sec. cm.$^{-5}$ while breathing 99 to 100 per cent oxygen. The average pulmonary vascu- lar resistance declined from 635 to 500 dynes sec. cm.$^{-5}$ with the change of conditions (fig. 3). This decline was not demonstrably re- lated to the values for either mean pulmonary artery pressure or pulmonary blood flow that were recorded while the patients breathed air fig. 4). No relation between the ages of the patients and either the absolute levels or the magnitude of the changes of resistance on

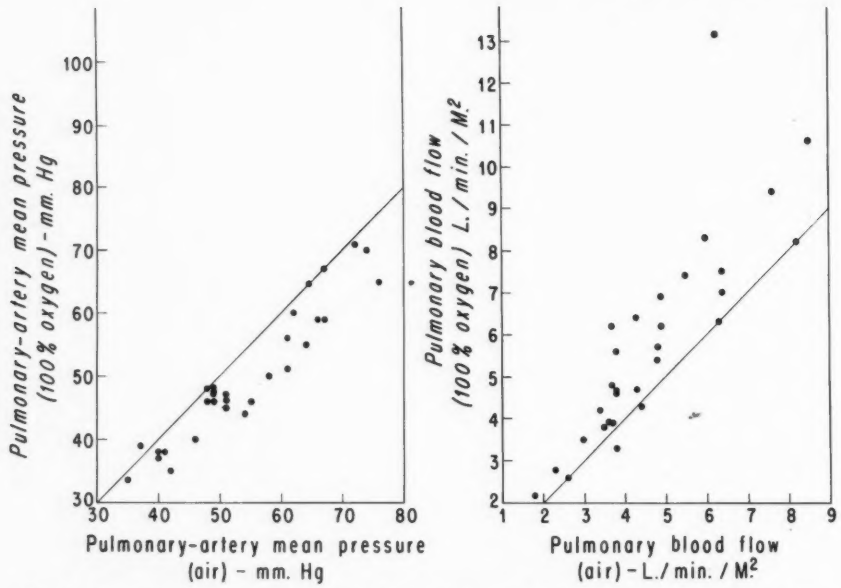

FIG. 1. Comparison of pulmonary artery mean pressure and pulmonary blood flow values obtained while breathing air (*abscissa*) with values obtained while breathing 95 to 100 per cent oxygen (*ordinate*). Note the fall in pressure and increase in flow under latter circumstance.

breathing oxygen could be demonstrated. The average systemic resistance (mean systemic artery pressure divided by systemic blood flow) increased from 1,460 to 1,650 dynes sec. cm.$^{-5}$ during the period of oxygen breathing. Random changes of considerable magnitude were seen in right atrial pressures of a few patients.

In 6 cases that included necropsy the status of the pulmonary vessels was graded independently according to the severity of structural changes.[12] The severity of these organic vascular changes was found to have a positive correlation with the pulmonary-systemic resistance ratio recorded during breathing of air and with that recorded during breathing of oxygen. However, in this small group of patients no definite correlation was found between the grade of vascular disease and either absolute or relative changes in pulmonary vascular resistance on breathing oxygen.

DISCUSSION

These data indicate that in patients with pulmonary hypertension and atrial septal defect the change from breathing air to breathing 100 per cent oxygen is nearly always associated with an increase in the flow of blood through the pulmonary circuit and a decline in pressure in the pulmonary artery. Further, since changes in left atrial pressure are minor and random, the increase in blood flow and reduction in pressure indicate that a decline in pulmonary vascular resistance has occurred. Therefore it appears that the pulmonary vascular bed in patients with atrial septal defect responds to this stimulus in a manner similar to that of the pulmonary vasculature in patients with ventricular septal defect or patent ductus arteriosus and in normal subjects. Most likely the fall in resistance is due to dilatation of pulmonary blood vessels already open, or to opening of channels that have been closed.

Assumptions. Three assumptions have been made concerning the data. First, for the calculation of pulmonary flow it appears entirely reasonable to assume that among the 13 patients in whom oxygen consumption was not

letermined while breathing oxygen it was not less than it had been while they were breathing air. Calculated with these values, the changes in pulmonary flow were of the same order of magnitude as in the group of 17 from whom the data for both circumstances were available. Since a slight increase of oxygen consumption with the change had been demonstrated in that group, the assumption of constancy among the 13 actually tends to minimize the volume of their pulmonary blood flows.

Second, in the presence of atrial septal defect the close similarity of pressures in the 2 atria assumed in this study has been demonstrated by Dexter[13] and by others. In these patients the differences between mean pulmonary artery pressures and left atrial pressures were considerable, and the defects usually were of large size. In only 8 of the 30, however, did the pulmonary flow exceed the upper range of normal—a fact that implies the flow across the defect was not great in the majority of cases under study.

The final assumption concerns the values used for saturation of pulmonary vein blood. Desaturation of pulmonary vein blood is unusual in cases of atrial septal defect.[13] Confirmation that the significant desaturation of systemic artery blood seen in 21 of the 30 patients while they were breathing air was due to right-to-left shunting of venous blood was obtained from indicator dilution curves. Indeed, by this technic all the remaining 9 patients showed evidence of right-to-left shunting, though of magnitudes too small to be associated with desaturation of systemic artery blood, as is common in patients having atrial septal defect without pulmonary hypertension.[14] In only 1 patient did the magnitude of the right-to-left shunt as demonstrated by dilution curves appear insufficient to account for the desaturation of systemic artery blood; and in this case, as mentioned earlier, the saturation of pulmonary vein blood was found to be 93 per cent. With the support of measurements of the saturation of pulmonary vein blood in 6 patients, it was assumed that full

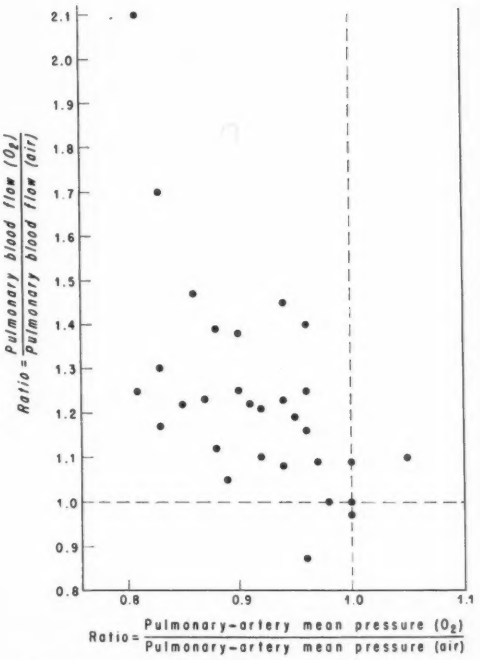

FIG. 2. Relation of change in pulmonary blood flow to change in pulmonary artery mean pressure on breathing 95 to 100 per cent oxygen. Values for pressure and flow during breathing of oxygen are expressed as fractions of values obtained during breathing of air. Dashed lines indicate unchanged pressure (*abscissa*) or flow (*ordinate*). A rough correlation between increase in flow and reduction in pressure is present.

oxygenation of pulmonary vein blood occurred in all other cases; and the values for oxygen saturations of hemoglobin and the average quantities of dissolved oxygen, as found in normal subjects under conditions of breathing air and breathing 100 per cent oxygen, were used in the calculations of pulmonary blood flow. Such an assumption could introduce a systematic underestimation of pulmonary blood flow during breathing of air, and hence might permit the estimation of an increase of pulmonary blood flow in response to oxygen when no such change in fact occurred. As outlined above, the available evidence makes this possibility an unlikely one, however; and independent collaborative data are provided by the consistent fall in pulmo-

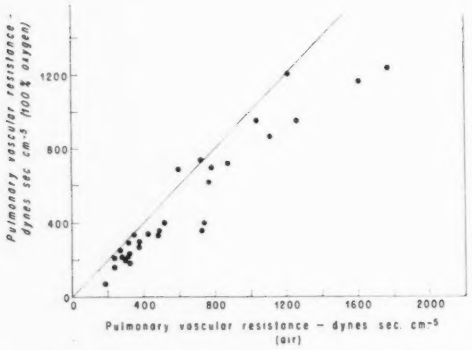

FIG. 3. Decrease in pulmonary vascular resistance on breathing 95 to 100 per cent oxygen. Note that this decrease occurs even in the presence of severe elevation of pulmonary resistance.

nary artery mean pressure associated with the breathing of 100 per cent oxygen (fig. 2).

Response of the Pulmonary Blood Vessels. The data are regarded as demonstrating a decrease in pulmonary vascular resistance associated with the breathing of 95 to 100 per cent oxygen in patients with pulmonary hypertension and atrial septal defect. The change in vascular resistance probably is not confined to those patients with pulmonary hypertension, since a decline in total pulmonary resistance which averaged 13 per cent has been found in 15 patients who had atrial septal defect without pulmonary hypertension.[15] This response is similar to that seen in patients having ventricular septal defect with or without pulmonary hypertension.[7] Further, the change in pulmonary artery pressure usually follows a similar time course, commencing within 15 seconds of the start of oxygen breathing and being virtually completed in 2½ to 3 minutes, which suggests that the underlying mechanism is similar in both conditions.

Vasoconstrictive Element. The significance of the present observations lies in the demonstration of a labile component of the pulmonary vascular resistance in patients with atrial septal defect and pulmonary hypertension, which component is affected by the concentration of oxygen in the inspired air. This apparent ability of the caliber of the pulmonary vessels to change implies the presence of a vasoconstrictive element in the increased vascular resistance seen in such patients. However, since similar changes in pulmonary vascular resistance occur in normal subjects and in patients having ventricular or atrial septal defects without pulmonary hypertension—although these are more difficult to demonstrate because of the lower absolute values for pulmonary artery pressures and pulmonary resistances—it is not possible to say whether the degree of tone of the individual smooth muscle fibers is normal or abnormal.

Studies of the effect of acetylcholine on the pulmonary circulation provide additional evidence for the contribution of vessel tone to the pulmonary vascular resistance in the presence of pulmonary hypertension in atrial septal defect. Harris[16] investigated 5 cases of atrial septal defect, in 3 of which pulmonary hypertension was severe. Injections of acetylcholine (average dose for a larger group, 2.3 mg.) produced no change in pulmonary artery pressure. However, when Shepherd and co-workers[17] studied the effect of continuous infusion of 2 to 24 mg. per minute of acetylcholine in 6 cases of atrial septal defect with pulmonary hypertension, both a fall in pulmonary artery pressure and an increase in pulmonary flow occurred. The greatest fall in resistance was observed when acetylcholine was infused during breathing of oxygen. Most probably acetylcholine caused dilatation of the pulmonary blood vessels by direct local action. The mechanism whereby inspired oxygen acts is not known.

Development of Pulmonary Hypertension with Atrial Septal Defect. Pulmonary hypertension associated with atrial septal defect differs from the hypertension associated with ventricular septal defect or patent ductus arteriosus in that it appears to be an acquired complication, rather than an immediate hemodynamic consequence of—indeed an integral component of the situation arising from—a communication between the pulmonary artery and aorta or between ventricles

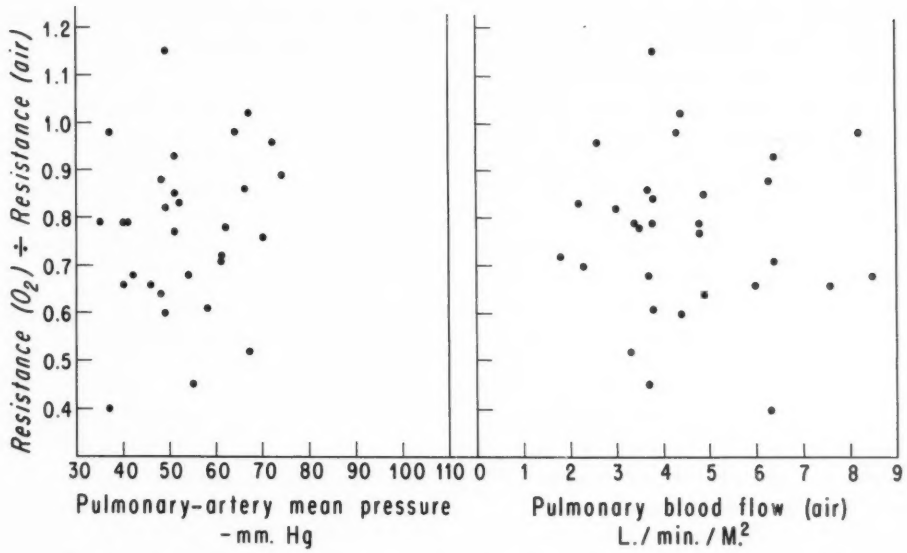

FIG. 4. Change in vascular resistance on breathing 95 to 100 per cent oxygen, related to pulmonary artery mean pressure and pulmonary blood flow values obtained during breathing of air. Note absence of any relation between the response to oxygen breathing and the basic levels of pressure and flow.

which is large enough to equalize pressures between the two circuits from birth. In our experience,[18] as in that of Dexter,[13] it is uncommon to find pulmonary hypertension of the levels discussed herein associated with atrial septal defect in patients less than 20 years of age. In certain patients, however, for reasons not understood, pulmonary artery pressure increases slowly or rapidly during early adult life, usually with persistence of an increased level of pulmonary blood flow. Development of hypertension in the pulmonary circuit, whether associated with increased pulmonary blood flow or not, is unlike the response of normal pulmonary vessels that dilate, with but a small change in pressure, when the flow through them is increased. This development of pulmonary hypertension in atrial septal defect with a raised pulmonary blood flow is associated with an increase in pulmonary vascular resistance from levels below the range of normal to values that equal or slightly exceed normal, with a considerable increase in pulmonary blood flow. Study of a relatively few patients seen over a period of 6 to 8 years suggests that once the level of pulmonary artery systolic pressure is significantly elevated, it may remain virtually the same while the progression of organic change in the pulmonary vessels is manifested only by a steady decline in pulmonary blood flow. Why pulmonary hypertension develops in certain patients and not in others is uncertain. Histologic studies of the small pulmonary vessels of such patients have shown that once pulmonary hypertension is established a distinct muscular media forms in the arterioles, and the media of the muscular pulmonary arteries hypertrophies. The progression of such changes seems identical to that of the changes in pulmonary hypertension associated with ventricular septal defect or patent ductus arteriosus, and hence the similarity of the responses of these vessels to dilating influences is not surprising.

Prognosis from the Tests. The prognostic significance of the change in pulmonary vascular resistance is uncertain, but the follow-

ing data suggest that a fall of considerable magnitude in the pulmonary vascular resistance when the patient breathes oxygen indicates a greater likelihood of immediate survival following surgical correction. While the mortality among patients with uncomplicated atrial septal defect is small[19]—less than 2 per cent—the finding of pulmonary artery systolic pressure in excess of 60 mm. Hg, or of total pulmonary resistance in excess of 50 per cent of systemic resistance while breathing air, is associated with significant increase in the rate of surgical deaths.[19] Seventeen of the patients herein considered underwent operation following cardiac catheterization in this institution. Of the 4 whose ratio of pulmonary resistance to systemic resistance exceeded 0.50, only 1 survived operation; of the 13 with ratios of 0.50 or less, 9 survived. Of 7 patients in whom the pulmonary vascular resistance during breathing of oxygen exceeded 80 per cent of the value obtained while breathing air, only 2 survived; but of the 10 in whom this ratio was less than 80 per cent, 8 survived.

In spite of the absence of a correlation between the histologic picture and the change in resistance on breathing oxygen, those patients in whom the pulmonary vascular bed shows evidence for a greater lability might logically be expected to have a less severe degree of organic pulmonary vascular disease. In such patients a more favorable long-term prognosis with regression of vascular disease might be anticipated. However, the number of follow-up studies is not yet sufficient for solving this aspect of the problem.

Summary

Pulmonary blood flows, and the pressure gradient across the pulmonary vascular bed, were measured in 30 cases of atrial septal defect in whom the pulmonary artery systolic pressure exceeded 60 mm. Hg, both while the patients breathed air and while they breathed 95 to 100 per cent oxygen.

The breathing of 95 to 100 per cent oxygen caused an average increase in pulmonary blood flow from 4.5 L. per min. per M.^{2} to 5.5 L. per min. per M.^{2} and an average reduction in pulmonary artery mean pressure from 55 to 5(mm. Hg.

The average calculated ratio of pressure t(flow (vascular resistance) across the lung de clined from 635 to 500 dynes sec. cm.$^{-5}$ Thi was interpreted to indicate dilatation of th pulmonary blood vessels.

The magnitude of the change in vascula resistance on breathing 95 to 100 per cent oxy gen was not related to the initial level of pul monary pressure or of pulmonary blood flow nor to the resistance values determined whe breathing air.

In a small group of patients for whom histologic sections of the lungs became available, the change in resistance on breathing oxygen could not be related to the severity of the vascular disease. Those patients in whom the breathing of oxygen caused the greater decline in resistance had a higher operative survival rate.

Summario in Interlingua

Le fluxos de sanguine pulmonar e le differentias de tension trans le vasculatura pulmonar esseva mesurate in 30 patientes con defectos del septo atrial in qui le tension systolic del arterias pulmonar excedeva 60 mm de Hg tanto quando illes respirava aere como etiam quando illes respirava inter 95 e 100 pro cento de oxygeno.

Le respiration de inter 95 e 100 pro cento de oxygeno causava un augmento medie del fluxo de sanguine pulmonar de inter 4,5 1/min/m^2 a 5,5 1/min/m^2 e un reduction medie del tension pulmono-arterial medie de inter 55 mm de Hg e 50 mm de Hg.

Le calculate proportion medie de tension a fluxo (= resistentia vascular) trans le pulmon descendeva ab 635 a 500 dyna/sec/cm^{-5}. Isto esseva interpretate como indication de un dilatation del vasos de sanguine pulmonar.

Le magnitude del alteration in le resistentia vascular, resultante del respiration de inter 95 e 100 pro cento de oxygeno non esseva relationate al nivello initial del tension pulmonar o del fluxo de sanguine pulmónar e non al valores del resistentia determinate quando aere esseva respirate.

In un micre gruppo de patientes ab qui ·etiones histologic del pulmones deveniva isponibile, le alteration del resistentia per le ·spiration de oxygeno non poteva esser rela- onate al severitate del morbo vascular. Le atientes in qui le respiration de oxygeno usava le plus grande reduction del resisten- ia se distingueva per le plus alte procentages e superviventia al intervention chirurgic.

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Studies Made by Simulating Systole at Necropsy

XII. Estimation of the Initial Cardiac Forces from the Ballistocardiogram

By Isaac Starr, M.D.

In a preceding communication[1] I have suggested that we are now in a position to look more closely at the higher dynamic aspects of cardiac function in our patients. From an analogy with common experience in automobiles, it is reasonable to expect that the first sign of myocardial weakness will manifest itself in diminished ability to accelerate the blood, that is, in diminished cardiac forces. In this study we aim to establish a clinical method of detecting abnormalities of the initial cardiac forces by means of the ballistocardiogram.

IN THE studies based on our cadaver experiments we have previously concerned ourselves with clinical methods of measuring the heart's output[2, 3] and its work,[4] aspects of cardiac function that could be measured, when systole was simulated, with an accuracy that cannot be attained during life. To complete this line of attack we needed a similar study of the cardiac forces, which, as far as I am aware, have never been measured during life. Such a study was of especial interest to me since the ballistocardiogram, as used in this laboratory, is a recorder of force.

From the first it has been realized that the ballistocardiogram does not give a true record of the cardiac forces throughout systole.[5] This is because, as systole progresses, secondary forces arise due to changes in direction and velocity of blood in the vessels. These secondary forces either compete with or reinforce the forces arising directly from the heart; so the ballistocardiogram secured during the later part of systole is the resultant of many forces. But one would expect that during a brief interval between the onset of ejection and the arrival of important amounts of blood at the aortic arch and the curve of the pulmonary artery, the ballistocardiogram would be related solely to the cardiac forces occurring simultaneously. This paper is concerned with developing a quantitative method of estimating these initial cardiac forces from certain aspects of that record.

Several considerations encouraged us to make this study. First, our theoretical views of cardiac dynamics[1] indicate that the forces concerned with the initial acceleration of the ejected blood should have great clinical importance in judging the strength of the heart; they produce what one might call the jerk of the contraction. Second, experience suggested that such a method would provide information of great clinical interest, for the I wave of the ballistocardiogram, occurring simultaneously with these forces, varies greatly from one patient to another, tending to be low or absent in many patients with heart disease. Finally, if the cardiac forces could be successfully estimated in our experiments, we would have a test of our method against known amounts—the ideal of all quantitative methodology—and we had every reason to expect such a comparison would at once disclose errors in our present conceptions regarding the genesis of the ballistocardiogram and permit us to seek for means of correcting them. Thus we could hope to define more exactly the influence of noncardiac factors, such as the height of the blood pressure, the distensibility of the vessels, and the size and structure of body tissues, on the ballistocardiogram, for there was already reason to believe that these might have some effect on the record.[6, 7]

The consummation of such a plan required the development of a quantitative method of

From the Department of Therapeutic Research of the Medical School of the University of Pennsylvania, Philadelphia, Pa.

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stimating the initial "cardiac" force applied n each of our 76 experiments. The "cardiac" forces could then be compared by statistical nalysis with the forces registered by that part of the ballistocardiogram that was recorded simultaneously, and with other features of this record.

Material and Methods

The technic of the cadaver experiments has already been described.[6] A high-frequency table ballistocardiograph was used and displacement was recorded, giving what is properly called a "force ballistocardiogram."

The clinical and autopsy findings of 6 of the 7 subjects used in this study have already been recorded.[2, 6] The other, a woman aged 50, height 159 cm., weight 41.5 Kg., had died from advanced scleroderma. We were thus provided with a unique opportunity to discover whether marked change in the physical properties of the tissues would have a noteworthy effect on the ballistocardiogram. The other 6 subjects were normal in this respect, and they exhibited considerable differences in body size and habitus.

Five subjects were perfused with blood and 2 with water, providing a total of 76 simulated systoles for study and analysis. The remainder of our data secured on subjects perfused with water we disqualified for 1 of 2 reasons: either these data fell into the period when we were having technical difficulties getting a proper I wave on the recorded ballistocardiograms, or they were secured in early experiments in which the speed of the moving film was too slow to permit measurement of the slopes as accurate as that which could be secured in later experiments in which the film moved twice as fast.

Of the data obtained from the 7 subjects studied we omitted those secured in only 1 systole, E.S. no. 11, because the time record showed that the film had slipped while systole was being simulated, and the slopes could not be accurately measured.

Measurement of the Record

Both the measurements and calculations are most easily explained by examples. Thus the record of curve 10 of subject E.S. has been redrawn in figure 1. The first step was to draw a line tangent to the ejection curve 0.08 sec. after the onset of ejection, and measure the angle (θ) of this constructed line with the horizontal.

After placing the base line of the ballistocardiogram the dimensions of the I wave were measured, its maximum depth being recorded to the nearest millimeter. A line was then drawn to coincide with the initial part of the H-I segment, and its angle with the horizontal was measured. These measurements were converted to absolute values by the corresponding calibrations, for example in curve 10 of E.S. we found

angle H-I = 70° tan H.I = 2.75

Calibration of the ballistocardiogram: 280 Gm. = 12.65 mm.

Time calibration: 1 mm. = 0.02 sec.

To bring this to our standard calibration, 280 Gm. = 10 mm., we correct the slope as follows:

$$2.75 \times \frac{10}{12.65} \times \frac{1}{0.02} = 109 \text{ mm. per sec.,} \quad (a)$$

which is the slope expressed in the relative units we routinely use.

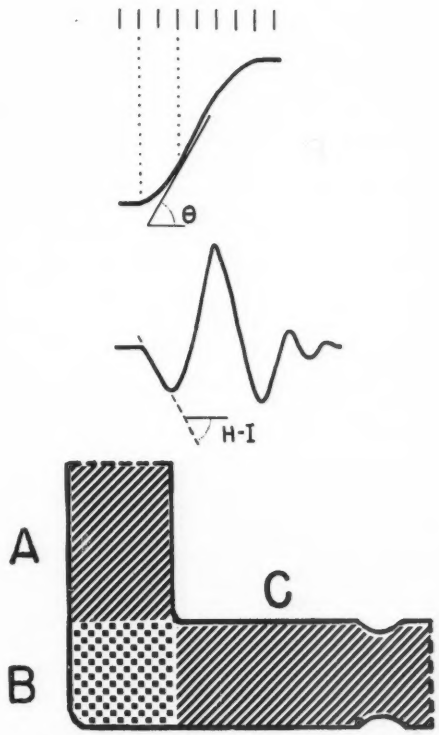

Fig. 1 *Top.* A scale drawing of the record secured on subject E.S. curve 10 to show the measurements made on all records.

Fig. 2 *Bottom.* Diagram of the aortic cannula with the fluid in it divided into 3 parts. The movement in two of these parts makes a contribution to the forces when systole is simulated. During the experiment the terminal limb of this cannula lies in the left ventricle's outflow tract and its tip is tied into the mouth of the aorta.

An estimate of the errors involved in measuring the slopes of our records was sought by remeasuring a sample of 22 records after the lapse of 2 months had removed all recollections of the value first secured. The 2 measurements of the same slope agreed within 1° in 82 per cent, within 3° in 91 per cent. The 2 remaining H-I segments were flat and rounded and it was more difficult to draw with accuracy the lines tangent to the initial part of the curves. However the angles measured were so small that their tangents differed very little, and the larger error of measurement did not introduce a larger error into the result.

Calculation of the "Initial Cardiac Forces"

To calculate the forces employed in our various simulations of systole, one must consider the fluid in each of the 2 glass cannulas, one tied into the mouth of the aorta, the other into that of the pulmonary artery, to be divided into 3 parts, as is shown for the aortic cannula in figure 2. The movement of fluid in part A (fig. 2), as well as that of the contiguous fluid upstream in the glass tubing connecting the cannulas and syringes, and the movement of fluid within the syringes themselves, does not concern us, as all this fluid was moving at right angles with the vector in which the ballistocardiograph was recording the forces.

Forces of the Terminal Limb

The calculation of the forces concerned with the movement of fluid in the terminal limbs of the 2 cannulas (fig. 2*C*) is best considered first because it presents no difficulties. In the record of E.S. 10 we found

$$\text{angle } \theta = 64° \text{ and } \tan \theta = 2.05$$

Calibration of the flow record: 1 mm. = 2.29 ml.
Calibration of the time record: 1 mm. = 0.02 sec.
The flow velocity at 0.08 sec. after start of ejection is therefore

$$2.05 \times \frac{2.29}{0.02} = 234 \text{ ml./sec.} \qquad (b)$$

And since there was no velocity at the start of the ejection, the average acceleration of flow during the first 0.08 sec. is

$$\frac{234}{0.08} = 2930 \text{ ml./sec.}^2 \qquad (c)$$

This fluid was being delivered through glass cannulas the diameter of which was 2 cm. Therefore the average linear acceleration of the injected fluid in both cannulas in 0.08 sec. in this experiment was

$$\frac{2930}{1^2 \times 3.14} = 933 \text{ cm./sec.}^2 \qquad (d)$$

The volume of the terminal limb of the aortic cannula, the limb which passed through the left ventricle and was tied into the root of the aorta, was 20.4 ml. That of the corresponding limb of the pulmonary artery cannula was 29 ml.

The total mass of blood concerned was therefore 49.4 Gm., the specific gravity of blood being close to 1.

The initial force concerned with motion of blood in the terminal limbs (fig. 2*C*) was therefore

$$933 \times 49.4 = 46{,}100 \text{ dynes approximately} \qquad (e)$$

Forces of the Turn

The movement of the fluid as it changes direction in the cannulas, at *B* of figure 2, is of great importance. Mr. George Peirce suggested that it could be calculated from our data as follows. The basic concept stems from the general formula

$$\frac{volume}{time} \times \frac{distance}{time} \times \frac{mass}{volume} = force \qquad (f)$$

For example from the record of E.S. 10 we found that at 0.08 sec. after the start of ejection the flow velocity is 234 ml./sec., since the radius of the tube is 1 cm. the linear velocity at 0.08 sec. is

$$\frac{234}{1^2 \times 3.14} = 74.5 \text{ cm./sec.} \qquad (g)$$

Since the density of blood is approximately 1, the third term of equation (*f*) can be neglected and we have

$$234 \times 74.5 = 17{,}440 \text{ dynes} \qquad (h)$$

Since the force at the start of ejection was zero the average turning force over the period of 0.08 sec. is approximately

$$\frac{17{,}440}{2} = 8{,}720 \text{ dynes} \qquad (i)$$

The turning force in both cannulas is twice this amount.

I must admit that I was slow to see the rationale behind this simple calculation of turning force, which takes no account of the characteristics of the turn, whether sharp or gradual. Accordingly, with the help of Dr. Askovitz I recalculated the forces of turning by a much more elaborate method taking account of the radius of the turn. But the result I secured was the same as that given above; so I was reconciled. I had failed to grasp the fact that if the turn is sharp the acceleration is great but the volume turning at any instant is small. If the turn is gradual the reverse is true. So the total turning force is independent of the radius of the curve.

The average forces applied during the initial 0.08 sec. of the simulation of systole in E.S. 10 was therefore the sum of the 2 groups of forces calculated above:

$$46{,}100 + 17{,}440 = 63{,}540 \text{ dynes} \qquad (j)$$

The initial forces applied in all the other systoles were calculated similarly, and the method should

give a good approximation of the average forces applied in our experiments during the first 0.08 sec. of ejection.

Forces Recorded by the I Wave of the Ballistocardiogram

By measurements on the photographic record we find in curve 10 of subject E.S.:

Distance from I wave tip to base line = 5 mm.

The calibration of the ballistocardiogram showed 12.65 mm. = 280 Gm. Therefore the force recorded at the I wave tip is:

$$5 \text{ mm.} = 112 \text{ Gm.}$$
$$= 112 \times 980 = 109{,}760 \text{ dynes} \qquad (k)$$

The I wave is so nearly triangular that it can properly be assumed to be exactly so. Therefore:

$$I \text{ wave force} = \tfrac{1}{2} I \text{ wave depth} \times I \text{ wave duration} \qquad (l)$$

and the average force during the I wave:

$$\frac{I \text{ wave depth} \times I \text{ wave duration}}{2 \times I \text{ wave duration}} = \frac{109{,}760}{2}$$
$$= 54{,}880 \text{ dynes} \qquad (m)$$

The same calculation was made in each of the other experiments.

Results and Discussion

As far as I am aware, this paper marks the first attempt to standardize a method of detecting the cardiac forces by means of a comparison with known forces. But it should be noted that I felt competent to do satisfactory quantitative work only where the situation is at its simplest, at the very beginning of ejection, when, for a brief period, the relation between cardiac forces and ballistocardiogram is, in theory, that of Newton's third law of motion. The primary aim of this study was to see how nearly this ideal situation obtained in our experiments and presumably would obtain during life. It was, therefore, necessary to set a time limit and we chose the first 0.08 sec. of ejection because this is the usual duration of the I wave in ballistocardiograms, which facilitates the comparison of force applied with force recorded.

Relation between Cardiac Force Applied in 0.08 sec. and Force Recorded in I Wave. Figure 3 shows the data secured in each of the 7 subjects, and in the whole group. The regression of all 76 experiments is shown in relation to the line of perfect agreement in

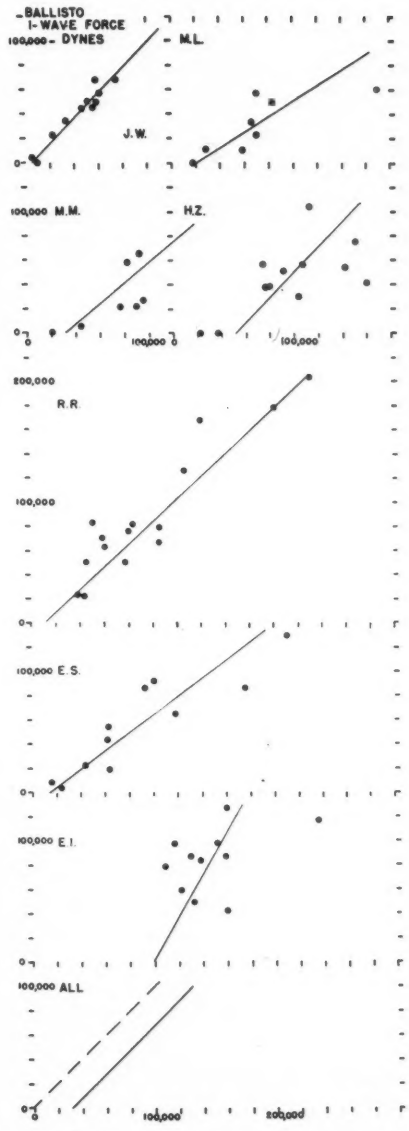

Fig. 3. Relation of the cardiac force applied in the first 0.08 sec. of ejection to the force represented by the I wave of the ballistocardiogram. Subjects E.S. and E.I. were perfused with water, the others with blood. The solid lines are the calculated regressions for each subject. At the bottom the regression of all the data, 76 simulations of systole, is shown as a solid line for comparison with the line of perfect agreement (*broken line*). The correlation coefficients and standard deviations are in table 1.

FIG. 4. Three ballistocardiograms which accompanied the same initial cardiac force but under conditions of greatly different pulse wave velocity. All from subject E.I., the curves, from left to right, are nos. 10, 11, and 9. The initial cardiac force was calculated to be 160,400, 159,600, and 160,400 dynes respectively in each. The corresponding pulse wave velocities are given under each of the records. The stroke volumes were 83, 63, and 55 ml. respectively; the femoral blood pressures 86/44, 203/106, and 287/153 mm. Hg; the duration of ejection 0.31, 0.22, and 0.20 sec. Note the diminution of the depth and breadth of the I wave as P.W.V. increases, but the slope of the H-I segment remains the same.

the lowest part of figure 3. The agreement between the 2 slopes is extremely impressive for the 2 lines are almost exactly parallel, that representing the estimates being somewhat lower than the actual forces applied. The regression equation is

$$\textit{Average initial force applied (dynes)} = 30{,}500 + 1.02\ \textit{(Average force of I wave, dynes)} \qquad (143)^{*}$$

The standard deviation about the regression is 32,200 dynes and the correlation coefficient 0.79 whereas a value 0.29 is significant[8] for $p = 0.01$. So there is no doubt that the relationship is a very strong one. This part of the ballistocardiogram is obviously in large measure determined by the cardiac forces acting simultaneously.

It is to be noted, however, that the recorded forces are lower than those applied, and one would expect this for several reasons. First, the glass cannulas lying in the outflow tracts of the 2 ventricles do not point directly headward but at an angle of about 30° from the longitudinal axis of the body. The recorded forces would be somewhat smaller than those applied for this reason alone. Second, our limit of 0.08 sec. does not exclude all the opposing forces due to blood movement in the aorta, as will be demonstrated later. Finally there is every reason to expect that, in passing through material such as the body tissues, mechanial energy would in part be converted into heat and so fail to appear in our force record. The difference, therefore, between the recorded and applied forces is readily accounted for; I was surprised that it is as small as it turned out to be.

Factors in the Scatter of the Data. Turning one's attention to the scatter shown in figure 3, one must first recall that I-wave depth was measured only to the nearest millimeter, and since these waves ranged from 0 to 14.9 mm. in depth,* the error of measurement from this source alone is considerable. Therefore it seems evident that in the data of subjects J.W., E.S., R.R., and M.L., the scatter about the regression is so small that the known errors of measurement are ample to account for most of it. But in the data of H.Z. and E.I. the scatter is very much greater. Searching for a reason for this difference, we discovered 3 experiments on subject E.I. in which the forces applied were almost identical but the I-wave depth varied 3-fold. The ballistocardiograms of these 3 experiments have been redrawn (fig. 4) to illustrate the differences among them. When the I wave was small the pulse wave velocity was several times that present when the I wave was larger. This suggests an explanation that can be tested in our data.

Do Differences in Vascular Elasticity Influence the Size of the I Wave? Such differences can be judged by the changes in pulse wave velocity which accompany them, so the answer to this question was sought by arranging the data into pairs, and 11 such pairs

*Regression equations of general interest have been given numbers in series with those obtained before from the data secured in these cadaver experiments. Other equations have been given letters.

*The apparent exception to this statement is due to a misprint. In subject R.R., Curve 9, the I-wave size, given as 17.5 mm. in table 3 of a previous publication,[7] was actually 7.5 mm.

TABLE 1.—*Influence of Pulse Wave Velocity on the I Wave and H-I Slope. Both Members of Each Pair Are from the Same Subject*

Subject and no.		Force applied $\times 10^3$ = dynes	Flow velocity at 0.08 sec. ml./sec.	Pulse wave velocity M./sec.	diff.	Force in I wave $\times 10^3$ = dynes	diff.	H-I slope mm./sec.	diff.
H.Z.	2	74	265	10.6		58		131	
	3	77	279	11.1	0.5	40	−18	97	−34
J.W.	8	55	210	5.8		45		110	
	5	55	210	6.6	0.8	46	+1	110	0
R.R.	4	81	284	6.2		77		140	
	15	84	292	7.5	1.3	81	+4	169	+29
M.L.	8	66	241	3.8		34		62	
	2	70	252	5.1	1.3	23	−9	43	−19
R.R.	3	61	228	5.3		63		110	
	1	60	223	7.1	1.8	70	+7	145	+35
J.W.	12	58	219	6.0		46		110	
	7	58	219	8.2	2.2	68	+22	143	+33
R.R.	13	46	184	3.8		45		73	
	11	44	176	7.0	3.2	22	−23	46	−27
H.Z.	7	112	361	6.1		106		188	
	8	107	349	11.1	5.0	58	−48	140	−48
E.I.	4	133	409	4.1		88		145	
	7	133	409	9.2	5.1	49	−39	135	−10
E.S.	10	63	234	4.3		55		109	
	4	64	236	9.8	5.5	19	−36	79	−30
E.I.	10	160	234	3.1		127		198	
	9	160	177	9.2	6.1	42	−85	174	−24

are shown in table 1. In each pair the subject is the same, the force applied very nearly the same, the flow velocity of injected fluid at 0.08 sec. after the onset of ejection is very similar, but the pulse wave velocities and I-wave sizes differ widely. By concerning ourselves with differences between the members of each pair we eliminate the major effect of the forces on the I wave and can hope to uncover minor effects such as might be caused by differences in vascular elasticity.

If the vascular elasticity has an effect on the amplitude of the I wave, the differences in pulse wave velocity shown in table 1 should be related to corresponding differences in I-wave size. The correlation between these 2 columns of differences in table 1 has a coefficient of 0.83, a level of 0.60 being significant for $p = 0.05$.[8] Therefore these results cannot be explained by chance and indicate that a noncardiac factor, the vascular elasticity, does influence the size of the I wave.

By another arrangement of the data of table 1 we can learn more about this relationship. For each of the 11 pairs we compute a difference in I-wave force per unit change of pulse wave velocity, and then ask ourselves whether these quotients bear a relation to the average flow ejected into the great vessels. This correlation is significant, $r = 0.66$, and the regression crosses the zero line at a flow velocity of 234 ml./sec. which is only a little below the mean flow velocity 261 ml./sec. used in these experiments. This means that differences in vascular elasticity have little or no effect on the I wave when the cardiac ejection velocity is small; but abnormally stiff vessels constitute a possible source of error in interpreting cardiac function from the ballistocardiogram when the stroke volume is large and flow velocity correspondingly high.

Therefore, while our results indicate that a factor other than the initial cardiac force may influence the size of the I wave, in com-

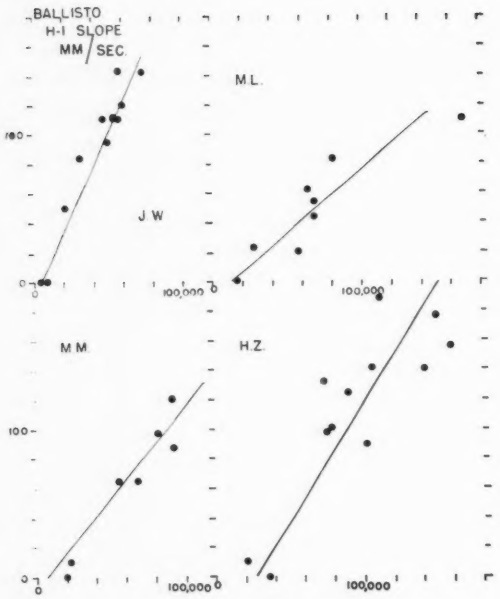

FIG. 5. Relation of "cardiac" force applied in 0.08 sec. to the slope of H-I segment of the ballistocardiogram. Data in 4 subjects perfused with blood. Note improvement in the scatter over that shown in figure 3. *Solid lines,* calculated regressions. Correlation coefficients and standard deviations are in table 1.

parison with the effect of the cardiac forces themselves, this second factor seems of minor importance. Nevertheless, we might improve our ability to estimate the initial cardiac forces by taking it into account. But it seemed far wiser to seek to avoid this interfering factor, rather than to attempt to correct for it, and this might be accomplished by moving the point of observation closer to the onset of ejection, to a time when still less blood had reached the aortic and pulmonary arches and produced opposing forces. Therefore we considered measuring the I-wave depth 0.02 sec. after ejection began. But for several reasons it seemed much better to take as our new starting point the initial slope of the H-I segment, that is, the tangent of the angle between the H-I segment and the horizontal, the H-I angle shown in figure 1. The implications of doing so must now be discussed.

On the Jerk of Cardiac Contraction. Since our ballistocardiograph is a force recorder, the slope of its record represents the first derivative of force, which is known to physicists as the jerk. As far as I am aware, the cardiac jerk has never been studied from the physiologic viewpoint and its quantitation presents many difficulties; our data are not exact enough to permit us to calculate the jerk with enough accuracy to make the effort worth while. So we cannot directly compare the slope of the H-I segment in each of our records with the aspect of "cardiac" performance which we believe to have brought it about. But our data do permit us to compare the H-I slope with the initial cardiac forces themselves and this relationship seemed well worthy of careful study.

Estimations of Initial Cardiac Force from Slope of the H-I Segment. At first thought an aspect of the record which represents the derivative of the recorded forces does not seem like a good starting point for a simple arithmetical method of estimating the forces applied; ordinarily one needs the calculus to define such a relationship accurately. But there is another way of looking at our problem. The deflection of the ballistocardiogram from the base line at any instant represents the force at that instant, so let us take as our starting point a measurement of I-wave depth made, not at the wave tip, but at a point on the H-I segment a very short time *(T)* after the beginning of ejection. Let us use the same *(T)* for this measurement in each experiment.

Then

$$\textit{Depth of the I wave at } T = \textit{(slope of the H-I segment)} \times T \qquad (n)$$

We plan to explore our data by regression technics and could use either side of this equation as the starting point of a method of estimating cardiac force. When one uses the right side, one may omit the time factor *(T)* because it is a constant throughout all the experiments and so its value would be automatically taken care of in the calculation of the regression equation. Therefore, in this particular case, measurements of the slope of the H-I segment make as good a starting point for a method of estimating cardiac forces, as

would measurements of I-wave depth made at a predetermined time.

For several other reasons, the H-I slope makes a much better starting point than does a measurement of I-wave depth made at a given time. Any such measurement must be made from the record's base line so the error of placing this base line is included in the unavoidable errors of measurement. In some records the base line is difficult to place with certainty and this is far more often true in records secured in the clinic than in those of our cadaver experiments. By using the slope of the H-I segment the error involved in placing the base line is altogether avoided. The considerable error inherent in identifying the exact time of onset of ejection, if one must place the time of the observation, is avoided also.

Figures 5 and 6 show the relationship between the initial forces applied and the slopes of the H-I segments of the resulting ballistocardiograms. The use of the H-I slope instead of the area of the I wave improves the correlation in every subject and also in the group as a whole (table 2). The improvement is especially conspicuous in the data from subjects E.I. and H.Z., on which the method based on I-wave area did very poorly. In each of the 7 subjects shown in figures 5 and 6 the scatter is now so small that it seems likely that the unavoidable errors of measurement account for it. The correlation between change of pulse wave velocity and change of H-I slope in the pairs illustrated in table 1 is not significant; so, if any error due to differences in vascular elasticity remains, we are unable to demonstrate it.

In figure 7 the regressions found in the data of each subject have been placed for comparison with that of the whole group of 76 experiments. This regression equation of the whole, when, in the vertical dimension of the record, 10 mm. = 280 Gms., is as follows:

Initial cardiac force applied, dynes =
18,000 + 603 *(slope of the H-I segment, mm./sec.)* (144)

The standard deviation around this regression is 28,100 dynes and the correlation coefficient is 0.85 whereas a value of 0.29 is significant for $p = 0.01$. The regressions of the individual subjects are very nearly parallel with the exception of that of M.L., which, pulled off by 1 divergent point, is not signifi-

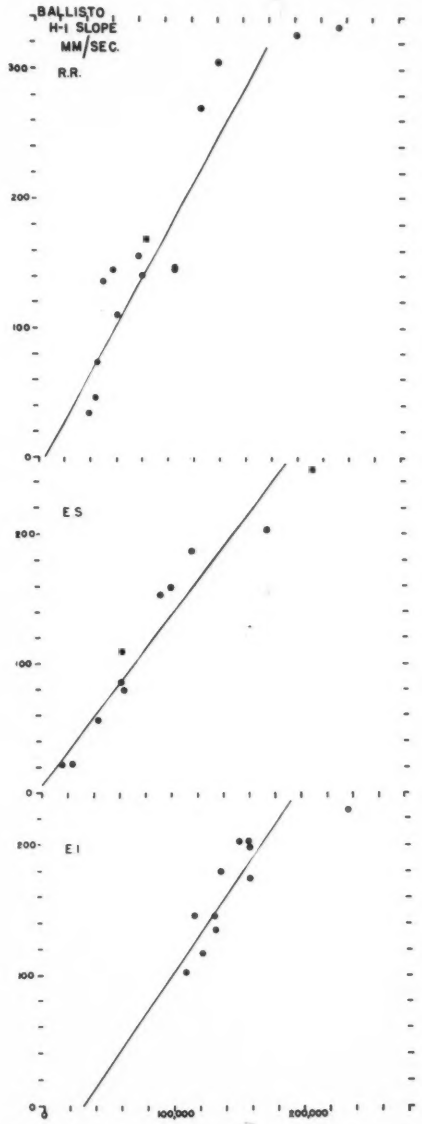

FIG. 6. Same as figure 5. Three more subjects, R.R. perfused with blood, E.I. and E.S. with water. The correlation coefficients and standard deviations are in table 1. Note the improvement over figure 3 especially in E.I.'s data.

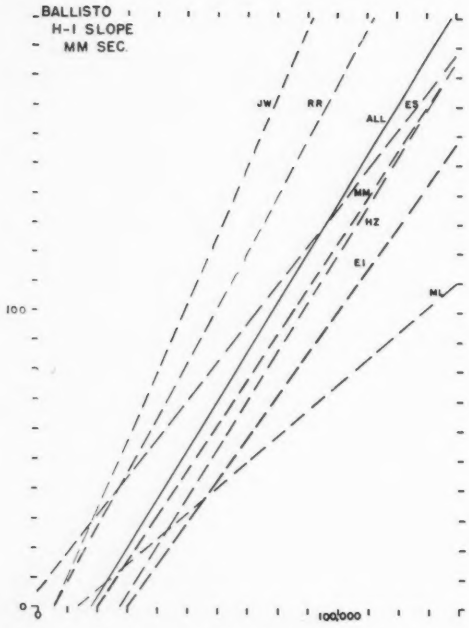

FIG. 7. The regression of the data on each of the 7 subjects shown in figures 5 and 6 (*broken lines*), and that of the whole group (*solid line*). Note the similarity of the slopes. That of the regression of M.L. pulled off by one bad point, is not significantly different from the others.

cantly different from the others. So the slopes of the regressions seem as equal to one another as we have a right to expect considering the methods at our disposal.

Possible Factors in the Scatter. Obviously a large part of the scatter of the group as a whole is due to differences between one subject and another. Before seeking an explanation for this, we should first point out a difficulty inherent in our experiments. The position of the glass cannulas tied into the mouths of the great vessels in each subject is very critical. When, in certain early experiments,[6] these cannulas were passed too far into the great vessels, simulation of systole produced no I wave at all. In later experiments, we made every effort to tie each cannula exactly in the mouth of its vessel, but it seems likely that there was enough difference of technic from subject to subject to have

TABLE 2.—*Comparison of Two Methods of Estimating Initial Cardiac Force from the Ballistocardiogram*

Subjects	No. of exps.	Estimations from I wave σ_r *dynes*	r	Estimations from H-I slope σ_r *dynes*	r
J.W.	12	6,100	0.96	5,500	0.96
M.M.	7	15,900	0.83	8,100	0.96
R.R.	15	20,300	0.93	21,900	0.92
H.Z.	12	30,300	0.67	21,500	0.85
M.L.	8	26,100	0.79	18,100	0.91
E.I.	11	29,500	0.43	18,000	0.84
E.S.	11	25,200	0.90	15,900	0.96
All	76	32,200	0.79	28,100	0.85

Standard deviation of cardiac forces used around their own means 52,900.

some effect on the I wave's size. Such a technical error would manifest itself in our results as a difference between one subject and another. For this reason the differences found between subjects in our experiments may well be larger than those to be expected during life.

The fact that some of the differences found may be due to technical difficulties does not relieve one of the duty to explore the data for factors related to body size and quality, which might account for the remaining differences between one subject and another. Subject E.I. died of advanced scleroderma and the physical properties of much of her skin differed greatly from those of our other subjects. The results secured on this subject were not conspicuously different from those of our other subjects but the omission of her data does slightly improve the scatter of the remainder, as is shown in table 3. Whether the subjects were in rigor mortis or not made no demonstrable difference to our results.

Looking for effects of differences in body size, we first investigated the correlation between the forces applied and 3 products: H-I slope and body weight, body surface area, and height. The results are given in table 3. We made no significant progress in reducing the scatter by this method, a result which might have been anticipated by noting how parallel were the regressions in figure 6.

Another type of adjustment for body size can be made by calculating multiple regres-

sion equations which employ the H-I slope and the subject's height or body surface area to estimate the cardiac force applied. These were calculated by Dr. Schild and are as follows:

Initial cardiac force applied, dynes =
$-164{,}000 + 580$ *(slope of H-I segment, mm./sec.)* $+ 1100$ *height, cm.* (145)

Initial cardiac force applied, dynes =
$-57{,}300 + 595$ *(slope of H-I segment, mm./sec.)* $+ 44{,}000$ *body surface area, M.*^{2} (146)

The standard deviations about these regressions have been given for comparison with the other results in table 3. The gain in accuracy secured by correcting for differences in body size seems too small to be worth while at the present stage of our knowledge.

Despite our inability to improve the method further at this time, it seems obvious that the slope of the H-I segment affords a rough clinical method of estimating cardiac forces with an accuracy more than sufficient to permit one to take the first quantitative step; that is, to divide the field into three parts; normal, above normal, and below normal; and to identify the position of any subject in this field with a chance of error reasonably small. When interested in changes in single subjects we should do much better than this. And one should point out that this method works well despite large differences in other physiologic functions. Thus in the data from the 76 simulated systoles analyzed for this study the stroke volume varied from 83 to 18 ml., the blood pressure from 282/139 to 42/29 mm. Hg, great differences in the elasticity of the great vessels are indicated by pulse wave velocities varying from 13.0 to 3.1 M./sec., the cross section area of the aortas varied from 10.8 to 2.5 cm.^{2}, the viscosity of the injected fluid varied from that of blood to that of water, 2 subjects had very sclerotic aortas, and in 3 the aortas were altogether normal; and these profound physiologic and anatomic differences had little if any effect on the relationship studied.

Relation of New Data to Previous Findings. Better estimation of the forces inherent in our simulations of systole has thrown new light on one of our previous findings. That the amplitude of ballistocardiograms is closely related to the acceleration of flow of the ejected blood was discovered early in these studies,[7] and we naturally concluded that this record was determined by the cardiac forces. But in these early studies[7] the square root of the ballistocardiogram amplitude, or of the areas of the I and J waves, was even more closely related to the acceleration of flow. Prof. H. C. Burger first pointed out to me that this finding was hard to reconcile with the obvious fact that the mechanical construction of our ballistocardiograph was such that one would expect it to record the forces directly, and so have a linear relation to them.

The explanation for this discrepancy is now at hand. In our former studies[7] we had assumed that the maximum flow velocity, the integral of the acceleration of the blood ejected in our simulations of systole, had a direct linear relation to the forces applied. Estimates of the forces themselves, described in this paper, demonstrate that this is true of only part of the force applied, that due to

TABLE 3.—*Are Methods of Estimating Cardiac Force from the Ballistocardiogram Improved by Considering Differences in Body Size and Constitution?*

Subjects	No.	Basis of method	Type of regression	or dynes
All	76	H-I slope	Simple	28,100
All	76	H-I slope × Body Surface Area	Simple	28,300
All	76	H-I slope × Body Weight	Simple	31,900
All	76	H-I slope × Height	Simple	27,400
All except E.I.	65	H-I slope	Simple	26,000
All except E.I.	65	H-I slope and Height	Multiple	24,200
All except E.I.	65	H-I slope and Body Surface Area	Multiple	23,700

Standard deviation of initial cardiac forces used (except E.I.) around their own mean 49,000.

movement of fluid in the terminal limb of the cannulas; another part, the force of turning, varies with the square of this velocity. So our previous assumption, close to the truth when the forces applied were small or moderate, led to a serious underestimation of the forces when they were maximal, and taking the square root of measurements made on the ballistocardiograms, by having its chief effect on the largest, improved the correlation. In the data described in this paper taking the square root of measurements made on the ballistocardiograms does not improve the correlation with the forces that originated them.

In a previous study[1] of the pulse we reported very strong correlation ($r = 0.92$) between a product, the maximum ejection velocity of the aortic blood × mean aortic blood pressure, and the maximum slope of the femoral pulse wave front. We have now tried the effect of substituting the initial cardiac forces for the maximum ejection velocity in the relationship with the pulse wave front given above. The correlation coefficient of this second relation was 0.85, which, when tested by Fisher's z transformation,[8] is found not to be significantly different from the value ($r = 0.92$) obtained before. Obviously, the slope of the advancing pulse wave front is closely related both to the maximum velocity of the ejected blood and to the forces which bring about this velocity.

In a preliminary report[9] of the present study on the ballistocardiogram we concerned ourselves with the relation between the slope of the H-I segment and the initial acceleration of the injected blood, and, after an adjustment for differences in body size, found very strong correlation between the two ($r = 0.88$). In this presentation we have concerned ourselves with the forces that bring about this initial acceleration. These are also closely related to the slope of the H-I segment and, without an adjustment for differences in body size, the correlation is 0.85, which is not significantly different from that of the relationship studied before.

General Considerations. Many more doctors will interpret ballistocardiograms from inspection than from measurement, and for these our results can be summarized as follows. Under most clinical conditions the normality of initial cardiac forces can be judged from the depth of the I wave. However, if the cardiac output is large and the pulse wave velocity is unusually great, the I wave may be diminished in amplitude although the cardiac forces are strong. Fortunately the likelihood of an error of interpretation is small, for this unusual situation can be recognized at a glance; in our records an I wave, small despite large initial cardiac forces, is always followed by a large J wave. In contrast, when the I wave is reduced by cardiac weakness, the J wave is reduced also.

If one bases one's judgment of the initial cardiac forces on the slope of the H-I segment, the error caused by differences in vascular elasticity is either minimized or avoided. So in reading ballistocardiograms routinely it is important to examine the record carefully for the sharp footward break of the H-I segment, which is such a conspicuous feature of normal records. If this sharp footward break is not found at the time of the onset of ejection, or if its usual steep slope is replaced by a more gradual one, this is strong evidence that the heart under study is not contracting with the jerk characteristic of hearts in good health.

Comparison between Pulse and Ballistocardiogram as Method of Determining Heart Strength. Some of our studies made by simulating systole at necropsy have been concerned with the pulse, others with the ballistocardiogram. In the last of those concerned with the pulse,[1] I pointed out the drawbacks inherent in any pulse wave method of estimating cardiac function. In this paper, which may well be the last of the long series, I should do the same for the ballistocardiogram. Both methods give important information about cardiac function, and there are certain advantages and disadvantages inherent in each of them.

We have been unable to establish satisfactory quantitative relations between pulse

wave and cardiac function from records taken by apparatus pressing on the skin over an artery, because such transducers are so difficult to calibrate in terms of pressure within the vessel. So we have been forced to puncture an artery to do quantitative work, a technic far less satisfactory for routine clinical work than is that of securing a ballistocardiogram.

Under certain conditions the ballistocardiographic method encounters difficulties which the pulse method avoids. These are chiefly concerned with uncertainties which arise concerning the contribution of the two sides of the heart to the ballistocardiogram. While the contribution of the normal left heart to the ballistocardiogram outweighs that of the right by a ratio of 5 or 6 to 1,[10, 11] in disease this ratio might not hold. However asynchronism of the forces of the two sides of the heart can be readily recognized by abnormal notching of the ballistocardiogram and this should put one on one's guard. In contrast, the pulse is concerned with the function of the left heart alone, and so this confusion does not arise.

Considerations related to the size of the cardiac chambers and the energy expended before ejection begins affect both methods equally. An obstruction at the aortic valve would cause both pulse and ballistocardiogram to fall short of indicating the full strength put forth by the ventricle. When the obstruction is further out the ballistocardiogram has an advantage; for example, in coarctation of the aorta the pulse in the lower parts of the body may be abolished, but only the later systolic parts of the ballistocardiogram are influenced, leaving the I wave and the H-I segment, the parts of that record from which cardiac strength can be most safely judged, apparently altogether unaffected. And this part of the ballistocardiogram is likewise unaffected by the more peripheral obstructions, which may diminish or abolish the pulse wave in any artery.

Differences in the elasticity of the vessels have an effect on the I wave of the ballistocardiogram only if the vessels are unusually rigid and the cardiac output is high, and this is a minor disadvantage in judging myocardial function from that record; if one bases his judgment on the slope of the H-I segment, the difficulty is avoided. In contrast, knowledge of vascular pressure or elasticity is a sine qua non of every quantitative judgment of cardiac forces made from observations of the pulse.

Observations of the pulse, the blood pressure, and the ballistocardiogram comprise the only methods that at this time give any promise of affording doctors a routine estimate of the cardiac strength of their patients. They should not be considered as rival methods, but as methods complementary to one another. Neither is perfect and we will do well to secure all the information we can concerning the strength of the heart of our patients.

Summary

In 76 simulations of systole made on 7 cadavers, 5 perfused with blood and 2 with water, the "initial cardiac force" of the first 0.08 sec. of ejection has been estimated. By statistical analysis this force has been compared with the force recorded in the longitudinal axis of the body by the I wave of the ballistocardiogram taken simultaneously, and also with the slope of the H-I segment.

There is very strong correlation between the initial cardiac force applied and the average force recorded in the I wave of the ballistocardiogram. The regression is almost exactly parallel to the line of perfect agreement, but the force recorded in the I wave is smaller than the force applied. This difference can be readily accounted for.

By moving the point of observation closer to the onset of ejection the conflict with opposing forces is minimized, so the initial slope of the H-I segment affords a better measure of the initial cardiac forces than does the depth of the I wave.

Attempts to improve the estimation of the initial cardiac force from the ballistocardiogram by consideration of the subject's height and weight resulted in only a small reduction of the scatter; so body size is evidently a minor factor.

The initial footward deflection of the ballistocardiogram, the H-I segment, represents the reaction to the initial cardiac forces which accelerate the blood headward. Thus it is in essence an example of Newton's third law of motion, and the qualifications that must be made to this statement are minor in nature.

From the slope of the H-I segment one can estimate the initial cardiac forces, which cause the initial acceleration of the ejected blood, with an accuracy equal to that of many good clinical methods.

Certain limitations of the ballistocardiographic method are discussed, and compared with those inherent in quantitative estimations of cardiac function from the pulse.

ACKNOWLEDGMENT

I am indebted to Mr. George Peirce for a very important suggestion which led to great improvement in the estimation of the "cardiac" force applied in these experiments. I am also indebted to Dr. Albert Schild for the major part of the statistical analysis of these data. Dr. Anna Corbascio collaborated on the rest.

SUMMARIO IN INTERLINGUA

In 76 simulationes del systole effectuate in 7 cadaveres—5 perfusionate con sanguine e 2 con aqua—le "fortia cardiac initial" del prime 0,08 secundas de ejection esseva estimate. Per medio de analyses statistic iste fortia esseva comparate con le fortia registrate in le axe longitudinal del corpore per le unda I del ballistocardiogramma obtenite simultaneemente e etiam con le inclination del segmento H-I.

Il existe un multo forte correlation del applicate fortia cardiac initial con le fortia medie registrate in le unda I del ballistocardiogramma. Le regression es quasi exactemente parallel al linea de accordo perfecte, sed le fortia registrate in le unda I es inferior al fortia applicate. Iste differentia non es difficile a explicar.

Si on move le puncto de observation plus proxime al declaration del ejection, le conflicto con fortias opponente es reducite, de maniera que le inclination initial del segmento H-I provide un melior mesura del fortia cardiac initial que le profundor del unda I.

Essayos de meliorar le estimation del fortia cardiac initial ab le ballistocardiogramma per prender in consideration le altor e le peso del subjecto resultava in solmente un leve reduction del dispersion, de maniera que il deveni evidente que le dimensiones del corpore non es un factor importante in iste calculationes.

Le initial deflexion verso le pede in le ballistocardiogramma, le segmento H-I, representa le reaction al fortias cardiac initial que accelera le sanguine verso le capite. Assi nos ha hic in essentia un exemplo del tertie lege de motion de Newton, e le modificationes que debe esser applicate a iste assertion es de natura minor.

Ab le inclination del segmento H-I on pote estimar le fortias cardiac initial, le quales causa le acceleration initial del sanguine ejicite, con un grado de accuratia equal a illo de multe bon methodos clinic.

Certe limitationes del methodo ballistocardiographic es discutite e comparate con le limitationes inherente in estimationes quantitative del function cardiac ab le pulso.

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The authors report the results of mitral commissurotomy on 120 surviving patients of their first 131 operations. In this group 72.5 per cent either maintained an excellent result or continued to be significantly improved. Restenosis of the mitral valve occurred in 10 patients (8.3 per cent). Six of these patients were improved after the second operation. Arterial embolization occurred in 4 patients during the postoperative period of observation. This incidence represents one fourth the preoperative incidence. The functional status of the patient, his age, and the cardiac rhythm all play a role in the operative results. However, the anatomic status of the valve itself was the most important factor. When the valve was pliable and competent 17.5 per cent of the patients had a poor result, in contrast to a poor result in 47.5 per cent of those cases with an immobile valve or significant regurgitation. By present standards it is now recognized that many of the early operations did not accomplish complete opening of the valve. In particular, it is important to open the posteromedial commissure whenever indicated. At present, closed mitral commissurotomy still seems to be the procedure of choice for mitral stenosis. Perhaps when a satisfactory prosthetic replacement for the mitral valve is available, the patients with calcified immobile valves with regurgitation may become candidates for open-heart repair with the use of extracorporeal circulation.

KRAUSE

Arachnodactyly Heart

By F. S. P. VAN BUCHEM, M.D.

Arachnodactyly is often associated with cardiovascular lesions. Most frequent are aortic abnormalities but congenital anomalies of the heart may be present. Another cardiac lesion has been found in some cases of arachnodactyly.

ARACHNODACTYLY is often attended by cardiovascular affections. Most frequent among these are aortic abnormalities, in particular aneurysma aortae and aneurysma aortae dissecans, due to medionecrosis cystica. In one of the cases of aneurysm of the thoracic descending aorta observed by us the changes of medionecrosis cystica were present to a greater or lesser degree in the walls of the carotid, femoral, splenic, and renal arteries without the existence of an aneurysm at these sites. MacLeod and Wynn Williams[1] found them also in the branches of the aortic arch. These aortic aneurysms are usually localized in the first part of the ascending aorta and cause there such a dilatation of the aortic ostium that the aortic valves become insufficient.[1-12] Aneurysms of the pulmonary artery have also been observed,[3, 7, 12, 13] likewise based on medionecrosis cystica.[3] Steinberg and coworkers[14] found aneurysmal dilatation of the aortic sinuses in some of their cases.

Further, in about 10 per cent of cases[15, 16] coarctation of the aorta is found in arachnodactyly, and other congenital anomalies of the heart like atrial and ventricular septal defects may be present (table 1). We were able to demonstrate pulmonary stenosis by means of cardiac catheterization in 2 patients.[12]

Finally, another cardiac lesion was found in arachnodactyly, which does not belong to the categories mentioned:

CASE MATERIAL

A 21-year-old man complained for 6 months of shortness of breath and palpitation on exertion (climbing stairs, riding a bicycle). He also suffered from dizziness and seeing stars when rising from the lying into the standing position. He occasionally fell when he had to stand for a long time. He had never been ill before; in particular, he never had had rheumatic fever. He did not cough or expectorate, nor had he nocturia. The patient was a long, thin young man (height 1.83 M., arm span 1.96 M., body weight 60 Kg.) with slight development of subcutaneous fat and muscles (fig. 1). The blood pressure was 135/75 in the lying position, and 125/85 when standing. The pulse was regular, equal, and 80 per min.

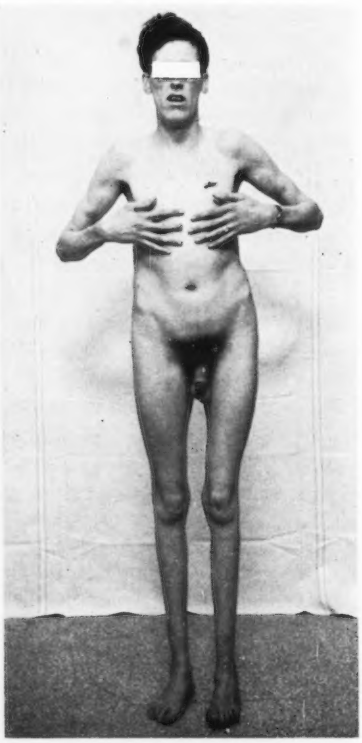

FIG. 1. Case 1.

His head was long and narrow, as was the nose; the palate was high and arch shaped. There was

From the Clinic for Internal Diseases, State University of Groningen, Groningen, Netherlands.

TABLE 1.—*Cardiovascular Lesions*

		Age (yr.)	Bone Age (yr.)	Height (M.)	Span (M.)	Weight Kg.	Disloc. lens	Aorta	Heart	17-keto-steroids 24 hr. (mg.)
J.K.	♂	10	13	1.54	1.63	32.6	+	—	arachnod.	10
		14	14	1.73	1.80	44.8			heart	
H.K.	♂	21		1.83	1.96	60	+	—	arachnod. heart	15
K.M.	♀	44		1.71	1.81	60	+	—	?	11.3
v.d.B.	♂	32		1.97	2.03	77.5	—	multiple aneurysm. aorta asc. + desc + art. pulm	aortic valv. insufficiency	10.1
V.W.	♂	13	17	1.92	2.02	65	—	aneurysma	—	8.8
		17	adult	1.97	2.15	76	—	aorta abd.	—	7.6
J.BR.	♀	23		1.70	1.85	48	+	isthm. st. dil. art. pulm.	L.V.C. sup. pulm. stenosis	9.3
T.W.	♀	33		1.70	1.78	53	—	aneurysma aorta desc.	—	4.1-8.3
d.G.	♂	27		1.86	2.0	67		isthm. sten.	aortic insufficiency	7.2
L.W.	♂	15	14	1.75	1.78	59	—	isthm. sten.		8.4
A.T.	♂	43		1.90	2.0	89	+	dil. aortae dil. art. pulm.	—	
P.F.	♂	16	13	1.86	1.86	54	—		pulmonary stenosis	9.8

no growth of beard or moustache. The venous pressure was not increased, the thyroid gland was not enlarged. The thorax was flat. The apex beat was palpable in the fifth intercostal space more than 1 fingerbreadth outside the midclavicular line, and it was heaving. A systolic thrill was also palpable there. On percussion cardiac dullness reached from the ictus cordis to the right sternal border. Apical auscultation revealed a loud systolic murmur with a third protodiastolic sound (fig. 2). The lungs were normal, the liver was not enlarged. The spinal column was kyphoscoliotic, due, according to the x-ray interpretation, to Scheuermann's disease. The extremities were particularly long in comparison with the trunk; the hands and fingers were tender and very long and narrow. The length of the middle finger was 12.5 cm. The patella was easily displaced on both sides. The patient could easily bend his knee to such an extent as to place the calcaneus against the buttock. He had a bilateral subluxatio lentis.

No abnormalities were found in the urine, in particular, there was no urobilin. There was a hypochromic anemia (hemoglobin 60 per cent, erythrocytes 3,600,000, leukocytes 8,500, diameter of the erythrocytes 7.2 μ, reticulocytes 0.5 per cent) and a histamine-refractory achylia gastrica. No occult blood was found in the feces. The basal metabolism was +1 per cent. Serum reactions for syphilis were negative.

Radiologically, the heart was spherical and enlarged (fig. 3). The aortic shadow was narrow. There were only slight pulmonary vascular markings. The circulation time was 12 seconds with magnesium sulfate. The electrocardiogram showed a normal PQ interval, QRS 0.12 second, and slurring RS in leads II, III, aV_F and V_6 (fig. 4).

On cardiac catheterization normal pressure values were found in the right heart (table 2).

Five years later he had been able to perform his office work regularly, but on exertion he rapidly became short-winded with palpitations. He did not cough and could lie flat without difficulty. Blood pressure was 115/90, the pulse was irregular, due to atrial fibrillation. The venous pressure was not increased, there was no edema or central cyanosis, but acrocyanosis was present. The heart had become much enlarged. The murmurs were as before

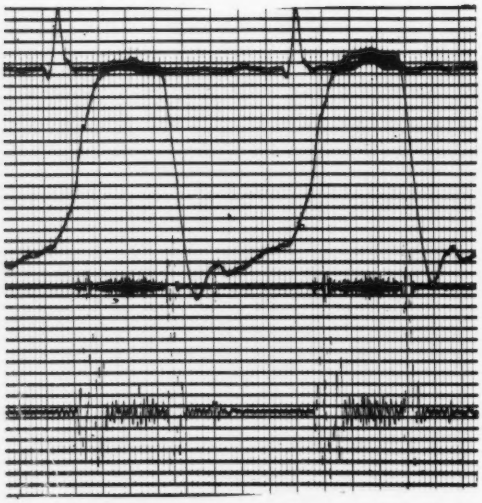

FIG. 2. Case 1. Electrocardiogram, apex beat, phonocardiogram, systolic murmur and third sound.

(fig. 2). The liver was not enlarged; the circulation time was 23 seconds with magnesium sulfate. The x-ray still showed slight pulmonary vascular marking. Both ventricles were considerably dilated.

A year later the heart showed even a more severe degree of dilatation (fig. 5). The other findings were unchanged. Some months later he developed bronchopneumonia and died with the signs and symptoms of heart failure. Autopsy, by Dr. Winkler and Dr. van der Horn, yielded the following findings. The heart weighed 780 Gm.; it was large and flaccid, with marked hypertrophy of left and right halves, dilatation of both atria and ventricles, relative incompetence of mitral and tricuspid valves (circumference of mitral ostium 23 cm., tricuspid ostium 18 cm.). The mitral valves were supple but thickened; the tricuspid valves were normal. The ductus Botalli was closed, and there was no septal defect. The coronary arteries were wide, the walls showed a slight sclerosis.

Microscopic examination, by Professor A. Arends, revealed hypertrophy with moderate connective-tissue proliferation in the myocardium (fig. 6). The abnormality of the mitral valves proved to be a fibrous thickening (fig. 6). The endocardium of the left atrium was thickened owing to proliferation of connective tissue without increase of elastic fibers.

These findings form no argument in favor of rheumatic disease.

A younger brother of the previous patient, 15 years of age, also showed the typical features of Marfan's syndrome with bilateral ectopia lentis. He had also pronounced dilatation of the heart. A

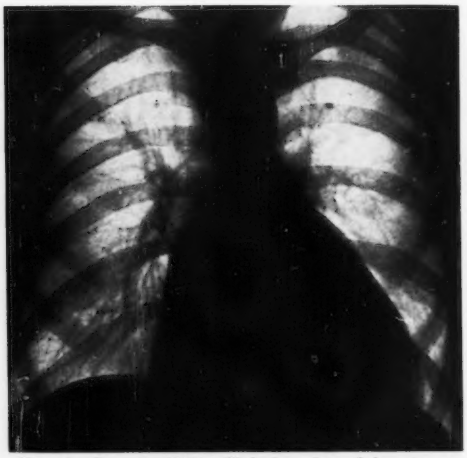

FIG. 3. Case 1, 1952. Globular shaped heart, poor pulmonary vascular filling.

systolic and a protodiastolic murmur were audible at the apex. On x-ray (fig. 7) the heart was spherical and enlarged, the vascular band was narrow, and pulmonary vascular markings were slight. The electrocardiogram showed a remarkable resemblance to that of his brother, with a QRS interval of 0.12 second (fig. 8).

Cardiac catheterization yielded normal values (table 2). Serologic reactions for syphilis were negative. Toxoplasmosis reactions: Sabin 1/96, complement-fixation test 1/4.

The mother (age 48 years) also showed the typical picture of arachnodactyly: characteristic hands (length middle finger 12 cm.) and feet, long narrow face with high-arched palate, and bilateral ectopia lentis. She was short-winded on walking quickly and riding a bicycle. Blood pressure was 150/80, the pulse was regular and equal. The heart was not enlarged. A systolic murmur was audible to the left of the sternum in the third and fourth intercostal spaces. Electrocardiogram showed a QRS of 0.10 second, slurring of RS in leads II, III, aV_F, and V_6, and ventricular extrasystoles. Five years later the heart was somewhat wider (Tr 1952: 12.4 cm.: in 1957, 13.5 cm.) (fig. 9). The toxoplasmosis reactions (Sabin and complement-fixation test) were negative.

Two boys died from unknown causes at ages 6 months and 4 years respectively. The father and the third son were normal (fig. 10). The father and mother were not related to each other.

RESULTS

The main abnormality found was therefore marked hypertrophy and dilatation of the left and right cardiac halves with relative insuffi-

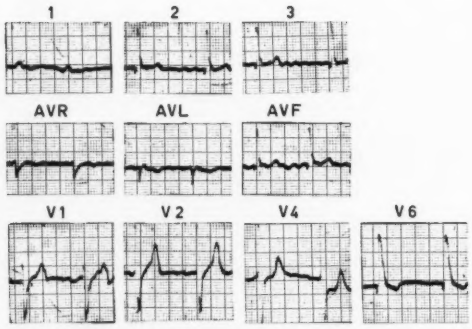

FIG. 4. Case 1. Electrocardiogram, bundle-branch block.

TABLE 2.—*Catheterization Data in Cases 1 and 2*

Patient age year	V. cava sup. Pressure (mm. Hg)	V. cava sup. O_2 sat. (%)	R. atrium Pressure (mm. Hg)	R. atrium O_2 sat. (%)	R. ventr. Pressure (mm. Hg)	R. ventr. O_2 sat. (%)
H. 21	5/0	68	8/3	68	28/0	75
J. 15	5/0	67½	5/0	68	25/0	68

	Art. pulmonalis Trunk Pressure (mm. Hg)	Art. pulmonalis Trunk O_2 sat. (%)	Art. pulmonalis Periphery Pressure (mm. Hg)	Art. pulmonalis Periphery O_2 sat. (%)
H. 21	28/8	25	10/5	100
J. 15	25/5	70		

ciency of the mitral and tricuspid valves and moderate fibrosis of the myocardium without valvular defects, thyrotoxicosis, hypertension, or disturbed coronary circulation. The relative insufficiency of the mitral and tricuspid valves was a result of the dilatation of the heart. Similar observations have also been reported by Whitfield et al.,[17] Taschen,[18] and Hedinger.[6] In these cases the great weight of the heart was a striking feature (in our case 780 Gm. at the age of 21 years; Whitfield 910 Gm., age 35 years; Hedinger 45 Gm., age 1 year).

As regards the clinical picture, it is remarkable that the patients have so few and sometimes even no complaints[18] even if the heart is already greatly enlarged. Taschen's patient died suddenly, as did his twin brother, at the age of 18 and a sister at the age of 18, in whom hypertrophy and myofibrosis cordis were also observed.

Whitfield[17] found aortic hypoplasia, namely, a circumference of the aorta of 47 mm.; in our patient, however, this was 60 mm., and in Taschen's patient 65 mm.

When we try to find the cause of this myocardial abnormality, we must first remark that no indications of myocarditis have been found, nor any evidence of any rheumatic change. It is sometimes mentioned (Futcher and Southworth[19]) that patients with arachnodactyly often develop rheumatic endocarditis. Study of the relatively small number of autopsies, however, shows that some valvular changes have often been observed, mainly thickening due to fibrosis, or pseudomyxomatous fibrous tissue, and sometimes the valves were "enrolled,"[1-5, 20-22] but no positive indications of rheumatic disease were found. Baer,[3] Tobin,[4] and MacLeod[1] also point out that there was no evidence of rheumatism.

The nature of these valvular defects is such that it does not afford an explanation for the hypertrophy. The values found on cardiac catheterization in our patient were also normal. When a valvular insufficiency was found, the cause was either dilatation of the aortic ostium (aneurysm of the ascending aorta) or ventricular dilatation, leading, therefore, to a relative aortic, mitral, or tricuspid insufficiency, respectively.

Indications of a myocardial toxoplasmosis[23] were not found. We did not find this in the myocardium. Our patient's brother, who also had an arachnodactyly heart, had only low titers (Sabin 1/96, complement-fixation test 1/4) and the serologic reactions were negative in the mother. The serologic tests for syphilis were negative. As in these patients we can speak of a familial cardiomegaly; we compared the picture with that found by Evans,[24] Gaunt,[25] Campbell,[26] and Brigden[27] in their patients.

These patients also had heavy hearts, and hypertrophy was found combined with usually extensive patchy fibrosis of the myocardium. In our patient, however, we failed to observe the "vacuolation" of the muscular fibers and of the conductive system, as observed by Gaunt,[25] Campbell,[26] and Bridgen[27]; Camp-

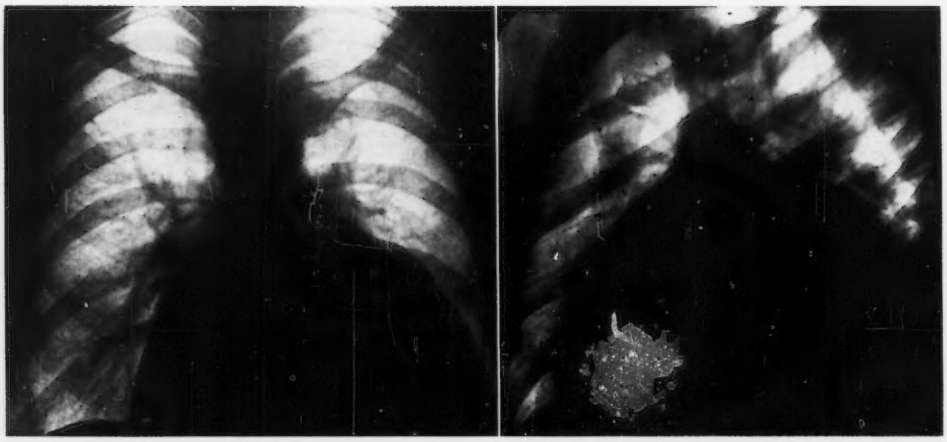

FIG. 5. Case 1. *Left.* 1957, progressive heart dilatation. *Right.* X-ray left oblique position.

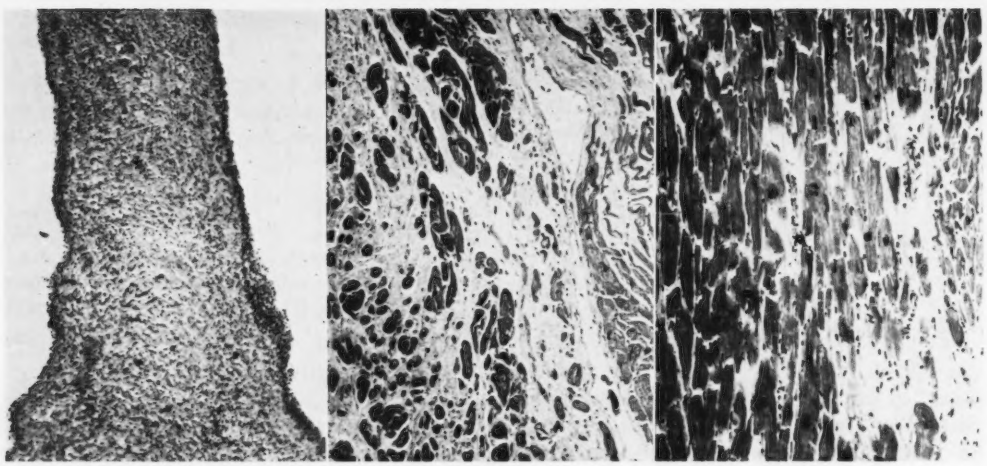

FIG. 6. *Left.* Thickened mitral valve. × 50. *Middle.* Myocardial fibrosis. × 112. *Right* Myocardial hypertrophy. × 112.

bell regarded this vacuolation as the most striking feature of this picture.

No valvular defects were found in these cases of familial cardiomegaly. In our patient the mitral valves were thickened, due to fibrosis, an abnormality which is not rarely found in patients with arachnodactyly, even if they have no myocardial abnormalities but an aortic aneurysm.

There are also some clinical differences, namely, the murmurs are only slight or may even be absent; further, the electrocardiographic changes, in particular the high voltage of the QRS complex, are more marked. Finally, none of these patients showed any indications of arachnodactyly.

In patients suffering from Friedreich's ataxia, large hearts with manifestations of bundle-branch block or changes of the T waves have some times also been found; associated hypertrophy and patchy fibrosis of the myocardium have also been observed.

Our patients had no symptoms of ataxia. Campbell[26] found no cardiac defects in the members of the family if they had no ataxia.

Our patient showed no indications of the

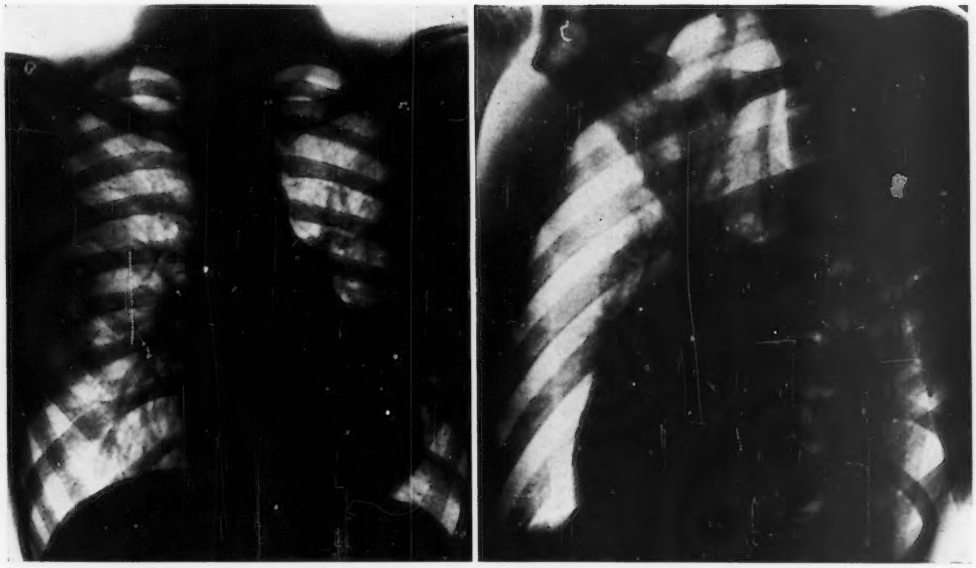

FIG. 7. *Left.* Case 2. *Right.* Case 2, left oblique position, dilated globular shaped heart.

glycogen disease of Von Gierke, in which only the heart may be affected.[28] Moreover, these patients die at an early age.

The literature of recent years contains descriptions of patients with enlarged heart, electrocardiographic changes, and manifestations of heart failure, for which no cause could be detected. Some of these cases showed at autopsy hypertrophy with a greater or lesser degree of fibrosis without extensive endocardial fibrosis or signs and symptoms of inflammation. This holds good for 2 cases of Evans[29] and patients 8 and 9 of Elster et al.[30] For these patients no indications of the familial occurrence of arachnodactyly were mentioned.

It appears from the above facts that patients with arachnodactyly without aortic defects or known congenital cardiac changes, may show a myocardial abnormality consisting of hypertrophy and fibrosis, finally leading to decompensation of the heart. Sometimes this also occurs in patients with arachnodactyly who suffer from an aortic aneurysm and aortic insufficiency.[4, 5 case 2, 11, 31] This is the reason why, when dealing with these myocardial lesions, we propose to speak of the arachnodactyly heart, in order to distinguish them from the other cardiovascular abnormalities attending arachnodactyly, and because such a picture is rarely observed elsewhere,[29, 30] It should be kept in mind that in an arachnodactyly family some members need not show all typical changes, but, for example, only an

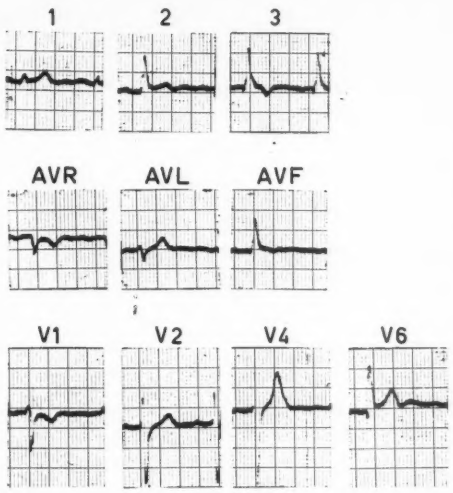

FIG. 8. Case 2. Electrocardiogram, bundle-branch block.

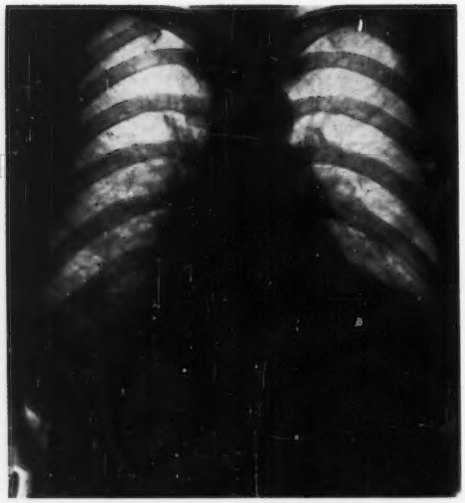

FIG. 9. X-ray mother of cases 1 and 2. Slightly dilated globular shaped heart.

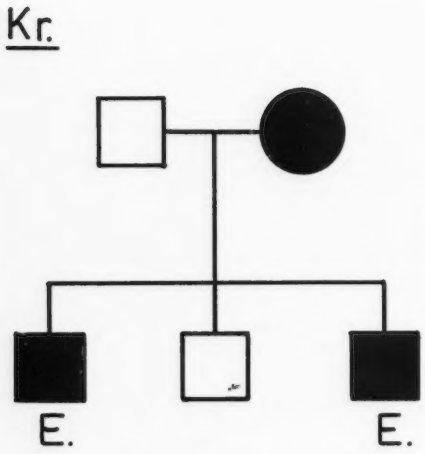

FIG. 10. *Open square*, normal male; *solid square*, male arachnodactyly; *solid circle*, female arachnodactyly.

ectopia lentis or aortic aneurysm. The family of these patients should therefore be searched for typical cases of arachnodactyly.[32]

In view of the association with arachnodactyly and the hereditary nature of this affection, a herditary predisposition for it should be accepted. It is a well-known fact that often fibrosis develops secondarily in myocardial hypertrophy. As Elster[30] remarked, the hypertrophy may "act deleteriously upon the intracardiac fluid and oxygen exchange and contribute to recurrent and progressive myofibrillar degeneration. An enlarging muscle mass contributes to impairment of muscle nutrition, for hypertrophy augments the requirements of the blood supply. This additive demand in the face of a decreased output resulting from heart failure compounds the problem of the failing myocardium."

As our patient showed only a moderate fibrosis, we believe it probable that the cardiac hypertrophy was primary. The following observation forms an argument in favor of this data.

In 2 other patients with arachnodactyly, who died as a result of rupture of an aneurysm of the thoracic descending aorta and of the abdominal aorta, respectively, we found moderate hypertrophy of the myocardium and no fibrosis. The direct cause of the hypertrophy is unknown. A relationship might be sought with the known increased activity of the epiphyseal disks, as in most cases these give rise to a striking longitudinal growth in the young patients (table 1).

SUMMARY

Aortic changes and congenital cardiac defects are often found in arachnodactyly. A rarer finding is a change of the myocardium (hypertrophy and greater or lesser degree of fibrosis) without other cardiovascular changes. A case is discussed.

A brother of the patient probably had a similar lesion. This lesion leads to marked cardiomegaly with relative insufficiency of the mitral and tricuspid valves. There are no indications of a rheumatic process. The hypertrophy is probably primary.

SUMMARIO IN INTERLINGUA

Alterationes aortic e congenite defectos cardiac se trova frequentemente in casos de arachnodactylia. Un constatation minus commun es un alteration del myocardio—hypertrophia e plus o minus pronunciate grados de

fibrosis—sin que altere anormalitates cardiovascular es necessarimente presente. Un caso es presente.

Un fratre del patiente habeva probabilemente un simile lesion. Iste lesion resulta in marcate cardiomegalia con relative insufficientia del valvulas mitral e tricuspide. Nulle indicationes de un processo rheumatic es a notar. Le hypertrophia es probabilemente primari.

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SPECIAL ARTICLE

Staphylococcal Infections of the Heart

By SIDNEY COHEN, M.D.

A SPATE of publications attest to the concern of physicians throughout the world about staphylococcal infections. The manifold clinical problems created by these infections touch upon all medical specialties. Cardiologists, however, must be especially concerned in view of the propensity of staphylococcal infection for secondary localization in the heart; in such cases the outcome depends principally upon the response to therapy of the cardiac infection. Furthermore, patients with acquired valvular or congenital heart disease are uniquely susceptible to cardiac infection with staphylococci that are in other respects virtually nonpathogenic for man.

This review will be devoted principally to the biology of staphylococci related to pathogenicity and to antibiotic treatment. The clinical and pathologic features of staphylococcal infections, areas in which the state of our knowledge has not changed greatly, will be treated more summarily.

ASPECTS OF PATHOGENICITY IN STAPHYLOCOCCI

Criteria of Pathogenicity

Much experimental effort has been expended on defining reliable criteria of pathogenicity in staphylococci.[1] To some extent any assessment of pathogenicity is only an approximation, for a microbe's ability to cause infectious disease cannot be evaluated apart from the host's ability to resist infection. Human resistance to staphylococcal infection varies so widely that one may encounter fatal infections by staphylococci that are ordinarily nonpathogenic and trivial lesions caused by pathogenic staphylococci. Nevertheless division of staphylococci into these 2 groups is worthwhile, for even when infection is incited by a "nonpathogenic" staphylococcus, the clinical and pathologic features of the resultant disease differ significantly in most cases from that caused by a typically pathogenic strain.

Staphylococci isolated from lesions that stamp them as being unequivocally pathogenic for man are characterized usually by golden or orange pigment and the ability to produce in vitro a remarkable array of extracellular toxic or enzymic substances; these include coagulase, at least 3 hemolysins, a leukocidin active against human leukocytes, enterotoxin, hyaluronidase, fibrinolysin, phosphatase, lipase, enzymes mediating the fermentation of mannitol, as well as other compounds. In general the more virulent staphylococci, as assayed in mice, produce a greater number of extracellular antigenic, and presumably toxic, subtances.

The most conveniently determined and reliable evidence of pathogenicity is the production of coagulase.* This substance, in the

From the Department of Microbiology, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago, Ill.

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*The seventh edition of Bergey's Manual of Determinative Bacteriology defines the pathogenic species *Staphylococcus aureus* by the properties of coagulase production and mannitol fermentation, irrespective of pigment.[2] Strains reacting negatively in these tests are classified as *Staphylococcus epidermidis*. The clinician who has only recently become familiar with the earlier nomenclature—*Micrococcus pyogenes* var. *aureus* and *Micrococcus pyogenes* var. *albus*—is entitled to sympathy. To avoid confusion, in this article I have used the words "aureus" and "albus" to signify only the color of the staphylococcal colony.

presence of a co-factor found in human or rabbit plasma, induces the clotting of fibrinogen. It may be readily detected by inoculating a culture of the microorganism into a tube of diluted human or rabbit plasma. Coagulase-positive strains yield a clot usually within 3 hours, occasionally as late as 18 to 24 hours. A rapid slide test has been proposed for this purpose but it may not detect the same entity as the tube test.[3]

The production of alpha lysin, a hemolysin relatively specific for rabbit erythrocytes, correlates very well with clinical evidence of pathogenicity. In the opinion of some investigators it is a better index of pathogenicity than coagulase production. However staphylococci produce at least 2 other hemolysins (beta and delta lysins) with maximum lytic activity against erythrocytes of other species and poorer correlation with pathogenicity for man. Specific tests for alpha-lysin production are not usually performed in clinical bacteriology laboratories. Accordingly, the common laboratory report of a "hemolytic" staphylococcus without further qualification is ambiguous, and may be misleading when taken as an index of pathogenicity.

Although more than 90 per cent of pathogenic staphylococci are yellow in color, gray or white strains of staphylococci cannot be regularly dismissed as nonpathogenic without the danger of serious error. Occasionally such strains may produce coagulase and alpha lysin and be responsible for outbreaks of highly invasive infection. Furthermore, production of yellow pigment is not a very stable property of staphylococci, as is demonstrated by the ease with which albus variants, which still produce coagulase and alpha lysin, are obtained in vitro from typical pathogenic aureus strains. By the same token aureus strains should not be regarded ipso facto as being pathogenic.

Bacteriophage Typing

Although the toxic products of the staphylococcus are useful in defining pathogenic and nonpathogenic species, they do not provide a basis for subclassification of strains within either species. The advantages of a sharper characterization have been realized in recent years through the development of bacteriophage typing.[4] Coagulase-positive staphylococci may be classified into 4 broad groups, I to IV, according to their susceptibility to lysis by a battery of stock bacteriophages. More specifically, the bacteriophage type of a given strain may be described by the numerical designations of the bacteriophages to which it is susceptible (e.g., 42B/80/81/52). This procedure has yielded results of great importance. Significant biologic properties have been correlated with bacteriophage groups or types. Thus, penicillinase-producing staphylococci fall most often into group III and to a lesser extent, group I. Enterotoxigenic staphylococci occur principally in group III. Staphylococci isolated from the majority of a large group of cases of impetigo in England were found to be bacteriophage type 71. Evidently this type is biologically adapted to this special variety of parasitism. Since 1954 a previously unrecognized type, 80/81, has been found to be associated frequently with virulent staphylococcal infection, particularly in hospitals and often on an epidemic scale.

In addition to the light that it has cast on the biologic properties of certain strains of staphylococci, bacteriophage typing has become an indispensable epidemiologic tool in tracing the course of epidemic or institutional outbreaks of staphylococcal infection. In several instances it has been possible to trace series of cases of staphylococcal infection to a limited number of carriers of the bacteriophage type in question and to terminate the outbreak by removing the carriers.

Pathogenesis of Staphylococcal Infection

Pathogenicity implies the existence of mechanisms for microbial survival and multiplication within the host and for inflicting injury. Coagulase-positive staphylococci are able to grow in normal human serum, in which many nonpathogenic microbes including coagulase-negative staphylococci are inhibited. The resistance of coagulase-positive strains may be derived from inactivation of the serum

inhibitor by their growth products, for culture filtrates of coagulase-positive staphylococci destroy the nonspecific inhibitory properties of serum. The available evidence indicates that the effective agent is associated with coagulase.[5]

A basic pathogenic attribute of staphylococci is their ability to survive phagocytosis by human leukocytes. In contrast to other Gram-positive pathogenic cocci, staphylococci are readily phagocytized by human leukocytes. Coagulase-positive strains survive within leukocytes and eventually kill them. Indeed the leukocyte may serve the staphylococcus as protection and means of dissemination.[6] This property may be related to a leukocidin that has been demonstrated in culture filtrates of many coagulase-positive staphylococci (but not coagulase-negative staphylococci) and which is active in high dilution upon human leukocytes.[7] It appears to be formed in infections in man for antibodies to it appear in increasing titer in 80 per cent of patients with acute staphylococcal infections.[8] Another staphylococcal product, delta lysin, is also toxic to human leukocytes.[9] Its role in vivo is uncertain for its action is inhibited nonspecifically by proteins.

The ability of staphylococci to multiply in vivo is greatly dependent upon the tissue in which they are deposited, as is apparent from clinical observations of the distribution of staphylococcal lesions. Experimental studies of murine infections indicate that staphylococci persist in large numbers for variable periods of time in the lungs, spleen, and liver without development of lesions, while in the kidney coagulase-positive staphylococci continue to grow and form multiple abscesses.[6, 10] The biochemical tissue factors that determine these differences in growth patterns are obviously important but unknown.

The mechanism by which staphylococci damage tissue cells other than leukocytes is not understood. Staphylococci produce a toxin thought to be identical with alpha lysin, which causes necrosis when injected into the skin or death when injected intravenously in rabbits. It is possible that large collections of staphylococci may produce alpha lysin or other toxins in amount sufficient to damage tissues locally and to provide the systemic toxemia characteristic of very severe staphylococcal infections.

Specific antibodies fail to provide very effective defense against staphylococcal infections. They may furnish some protection however, for agammaglobulinemic patients who are deficient in antibodies, are prone to infections by staphylococci.

Host Factors and Resistance to Infection

The primary habitat of pathogenic staphylococci is the nasal mucosa of man from which the skin and the immediate environment are contaminated. Coagulase-positive staphylococci may be cultured from perhaps 25 to 50 per cent of normal adults and about 60 to 80 per cent of personnel in general hospitals. Accordingly, exposure to the staphylococcus is universal and especially intense in the hospital. Normal adults are highly resistant to infection. The occurrence of disease is often associated with conditions that breach epithelial barriers against the staphylococci or weaken the normal defenses against them in the tissues. Some clinically important conditions that facilitate staphylococcal infection are summarized in table 1.

Experimental, as well as clinical evidence demonstrates the potentiation of staphylococcal infection by factors that impair host resistance. In a study with subcutaneously inoculated human volunteers Elek found that the number of staphylococci required to produce purulent infection was reduced by a factor of as much as 10,000 if a silk suture was left in place with the microorganisms.[11] Furthermore the infection was much more severe and extensive in the presence of the suture. These experiments confirm strikingly clinical evidence of long standing that foreign bodies facilitate the establishment and persistence of staphylococcal infection.

In the experimental animal, appreciable and often striking changes in resistance to in

fection have been produced by a wide variety of procedures. Experimental staphylococcal or other microbial infections have been enhanced by quantitative or qualitative dietary deficiencies, hemorrhagic shock, the injection of polysaccharides or bacterial extracts (endotoxins), or by the administration of cortisone, thyroxine, dinitrophenol, or certain naturally occurring organic acids.[12] The depression of resistance engendered by some of these agents is of short duration, lasting only a few hours or days, and may be followed by a period of increased resistance. The mechanisms by which resistance is affected by these diverse agents must be manifold. Irrespective of mechanism, however, it is clear that host resistance is a variable property sensitive to a wide range of stimuli.

TABLE 1.—*Conditions Affecting Susceptibility to Staphylococcal Infection*

A. Factors facilitating the entry of the staphylococcus
   a. Break in the integrity of skin or mucosa, e.g., surgery, trauma, childbirth, cystoscopy.
   b. Indwelling intravenous catheters.
   c. Intravenous injection of nonsterile solutions, e.g., heroin addicts.
   d. Dermatoses.
   e. Antibiotics ineffective against the staphylococcus. By reducing the normal microbial populations these agents permit the proliferation of staphylococci on body surfaces to a degree permitting invasion and disease, e.g., staphylococcal enterocolitis and superinfections.
B. Factors reducing ability of the host to dispose of staphylococci within the tissues.
   a. Foreign bodies.
   b. Neonatal state.
   c. Influenza, e.g., staphylococcal pneumonia.
   d. Systemic disease.
      (1) Diabetes mellitus.
      (2) Leukemia, lymphoma, Hodgkin's disease, myeloid metaplasia.
      (3) Cirrhosis of the liver, especially in advanced cases.
      (4) Arterial insufficiency.
      (5) ? Advanced neoplastic disease.
   e. Valvular or congenital heart disease.
   f. Medication.
      (1) ACTH and glucocorticoid hormones.
      (2) Hematopoietic toxins, e.g., 6-mercaptopurine, folic acid antagonists, nitrogen mustard.
      (3) Ionizing radiation.

STAPHYLOCOCCAL ENDOCARDITIS

Clinical Features

Endocarditis is the commonest and most important type of staphylococcal infection of the heart. Also, staphylococci are the cause of about 20 per cent of bacterial endocarditis. This relatively high frequency of staphylococcal endocarditis is the result mainly of reduction in the incidence of other forms of bacterial endocarditis due to effective antibiotic treatment of the primary infections.

Current concepts of the pathogenesis of bacterial endocarditis imply that microbes circulating in the blood during transient bacteremias settle in certain specially vulnerable areas of endocardium or vascular endothelium where they grow and produce vegetations. The increased susceptibility to bacterial endocarditis conferred by anatomic abnormalities of the heart valves has been demonstrated in dogs with experimentally induced aortic insufficiency. In these animals endocarditis has been produced regularly by a single intravenous injection of staphylococci or streptococci.[13] However, another factor, perhaps related to the workload of the heart, may also be important in the pathogenesis of bacterial endocarditis. In dogs with large peripheral arteriovenous fistulas, bacterial endocarditis occurs frequently upon normal valves without the deliberate injection of bacteria.[14] Also, by prior exposure to the cardiovascular stress of living under conditions simulating high altitude, rats may be rendered highly susceptible to the development of endocarditis following intravenous injection of bacteria.[15]

The clinical setting in which staphylococcal endocarditis occurs is very variable. In some patients with acquired valvular or congenital heart disease, but otherwise in good health, endocarditis may begin without any obvious primary source of infection and without contact with hospital strains of staphylococci. Usually the diagnosis is not difficult and the likelihood of success in treatment may be rel-

atively good. In other patients, more often without obvious cardiac disease, but with some of the predisposing factors cited earlier, endocarditis may make its appearance secondary to staphylococcal infection at other sites. The illness is often contracted in the hospital environment and the attendant problems of antibiotic resistant strains of staphylococci and underlying disease make treatment more difficult and recovery less likely. In a third group of patients endocarditis may be only one of multiple metastatic foci in severe bacteremic staphylococcal infection and indeed may be an incidental and relatively unimportant teminal event. Accordingly, the term staphylococcal endocarditis does not define a uniform clinical entity. Questions of prognosis, prevention, and treatment cannot be treated meaningfully without reference to the clinical substrate in which the disease has occurred.

Staphylococcic endocarditis is usually a rapidly progressive typically acute endocarditis, but milder, more prolonged illnesses similar to subacute bacterial endocarditis are also seen usually with strains reported as *Staphylococcus albus* which may be inferred to be coagulase-negative in most cases. Infection by coagulase-negative strains almost always takes places on an existing cardiac deformity, whereas 40 per cent of cases of coagulase-positive staphylococcal endocarditis begin on a previously normal valve. An additional difference is that infarcts resulting from embolism in coagulase-negative staphylococcal endocarditis are usually bland in contrast to the septic infarcts characteristic of endocarditis caused by coagulase-positive organisms.

The clinical features of staphylococcal endocarditis are well known and require no elaboration.[16–18] They include fever, often with chills and evidence of severe toxicity. Signs of cerebral damage are common, including stupor, coma, nuchal rigidity, and hemiparesis. Petechiae, skin rashes, splenomegaly, and obvious peripheral embolization are relatively uncommon in patients seen reasonably early in their illness. Murmurs adequate to suggest the presence of heart disease, most often rheumatic valvular disease, may be heard in from 50 to 75 per cent of cases. Marked change in the character of a murmur or the appearance of a new murmur is a most helpful but relatively infrequent sign. Laboratory findings usually include a normocytic, normochromic anemia, slight to moderate polymorphonuclear leukocytosis, albuminuria, and microscopic hematuria.

Blood culture is the essential test to establish the diagnosis. Fortunately the blood culture is almost invariably positive in untreated staphylococcal endocarditis. However it may be negative after inadequate treatment, even though clinical signs of active disease persist. If the diagnosis is strongly suggested by clinical features, 6 blood cultures should be taken at 3-hour intervals before treatment is begun. In critically ill patients, where immediate treatment is indicated, it is desirable to take at least 3 blood cultures within a period of perhaps 1 to 2 hours. Excessive numbers of cultures add little to the likelihood of establishing a diagnosis. Each culture should be inoculated into at least 2 types of liquid media and, where possible, pour plates should be made with a sample of blood to permit enumeration of the bacteria in the blood. Contaminated blood cultures, often with coagulase-negative staphylococci, may be a source of confusion. They may be avoided by rigidly aseptic venipuncture and inoculation of the blood into the culture flask. Thorough sterilization of the antecubital skin with alcohol or tincture of iodine before the venipuncture goes far toward eliminating contaminated blood cultures.

Bone marrow cultures or arterial blood cultures add nothing to conventional venous blood cultures.

In the presence of positive blood cultures it may be difficult to decide whether the patient has endocarditis or uncomplicated bacteremia. Suspicion of endocarditis must be high, for 50 to 65 per cent of patients with staphylococcal bacteremia prove to have endocarditis

lso.[17] With rare exceptions staphylococcal acteremia in a patient with valvular or con-enital heart disease signifies endocarditis. Even in the absence of signs of heart disease, acteremia persisting for several days, or ecurrent bacteremia after antibiotic treat-nent should suggest endocarditis. Changing murmurs or peripheral emboli strongly sup-ort the diagnosis.

The spectacular development of cardiac urgery has brought in its train the hazard f postoperative endocarditis, almost invaria-ly caused by staphylococci. Bacterial endo-arditis after cardiac surgery often begins insidiously with low-grade fever and malaise. It may be easily confused with the postvalvu-lotomy syndrome with resulting delay in cor-rect treatment.[20] Early recourse to blood cul-ture is important for correct diagnosis. In a series of 1,889 cardiac operations, 20 cases of postoperative endocarditis were detected, of which 11 were diagnosed within 3 months of surgery.[21] In 45 per cent of cases the infecting organism was *Staphylococcus albus* coagulase-negative. Similar findings are reported by others.[22] It is possible that aortic valve sur-gery, whether in consequence of the nature of the procedure or the location of the lesion, may entail special risks of postoperative endo-arditis. Six cases of endocarditis were re-ported after operations on 150 cases of aortic stenosis and 4 cases following 33 operations on patients with aortic insufficiency.[21]

The striking influence of foreign bodies upon the establishment and persistence of staphylococcal infection has been demon-strated in the heart. Five cases have been re-ported of postoperative infection in relation o silk sutures in the heart or great vessels. Antibiotic therapy was unsuccessful but re-noval of the sutures was followed by prompt ecovery.[23]

Cardiac surgery is rapidly becoming more omplex and prolonged. Devices for extra-orporeal circulation and plastic prostheses resent new potential avenues for entrance f infection. Under these circumstances it eems probable that postoperative staphylo-coccal endocarditis will continue to be a source of concern to the cardiac surgeon.

Staphylococcal endocarditis of the right side of the heart has certain distinctive clinical features.[24] In a recent survey, 50 per cent of cases of right-sided bacterial endocarditis were caused by staphylococci. The important predisposing factors have been surgical opera-tions, cutaneous infection, indwelling intra-venous plastic catheters or intravenous injec-tions from nonsterile equipment by heroin addicts. The disease most commonly attacks the previously normal tricuspid or, less often, the pulmonic valve where it rarely induces murmurs. Right-sided endocarditis may also occur in patients with patent ductus arterio-sus, intraventricular septal defect, or other congenital lesions, and in these cases the usual murmurs are to be expected. Clinical and roentgenographic signs of pulmonary embol-ism and infection are common. Systemic em-bolization is naturally infrequent but may occur secondary to pulmonary vein thrombosis at the site of a pulmonary infarct.

Blood cultures are positive in more than 90 per cent of cases of staphylococcal right-sided endocarditis, in contradistinction to the lower incidence of positive blood cultures in cases due to alpha hemolytic streptococci.

The rapid development of important com-plications, often before treatment can be in-stituted, is in large measure responsible for the distressingly low rate of cure in staphy-lococcal endocarditis. Aggravation of valvu-lar deformity often leads to congestive heart failure, which may be fatal in spite of bac-teriologic cure. Grossly destructive lesions of the valves including perforation of valve cusps are common. They lead to rapid devel-opment of signs of valvular incompetence with correspondingly changing murmurs. In-tractable congestive failure follows.

Erosive lesions developing from aortic valvular vegetations may produce aneurysms of the sinus of Valsalva that may perforate through the interventricular or interatrial septum or cause rupture of the heart, usually in the anterior wall of the left ventricle.[25]

TABLE 2.—*Nature of Action of Antibiotics upon Staphylococci*

Bacteriostatic	*Bactericidal*
Tetracyclines	Penicillin
Chloramphenicol	Streptomycin
Erythromycin	Bacitracin
Oleandomycin	Neomycin
Spiramycin	Kanamycin
Novobiocin	Vancomycin
Ristocetin	

Abscesses may occur in the fibrous structure of the valve rings. These lesions communicate by a narrow tract with a valvular vegetation. They may be readily overlooked at autopsy if the valve rings are not carefully dissected. As Sheldon suggests, such lesions may well be responsible for certain otherwise inexplicable failures of treatment.[26]

Embolism to the brain accounts for the high frequency of neurologic signs in this disease and is a common cause of death. Coronary arterial embolism is the cause of the many focal necrotic and inflammatory myocardial lesions found so commonly at autopsy in staphylococcal endocarditis. Occasionally a large coronary embolism is acutely fatal.

Antibiotic Treatment

The aim is rapid killing of the infecting staphylococci. In view of the wide variation of antibiotic sensitivity of staphylococci an in vitro determination of antibiotic sensitivity is essential in each case, preferably by a quantitative tube-dilution method. Also, it is desirable that the test should assess the bactericidal capabilities of the antibiotic.[27] However, even without specific bactericidal tests, a satisfactory course of treatment may be selected from a simple sensitivity test and knowledge of the properties of the available antibiotics. A classification of antibiotics in terms of their typical modes of action upon sensitive strains of staphylococci is given in table 2.

Many factors difficult to duplicate in vitro may affect the lethality of an antibiotic agent under conditions prevailing in vivo. Obviously the antibiotic must be delivered to the microbe at the site of infection in appropriate concentration and for an adequate time without imposing the risk of excessive toxicity to the patient. This may be delayed in staphylococcal infections because of the lack of circulation in necrotic foci and in vegetations. Bacteria that are not multiplying, as may be the case in phagocytized organisms or in focal necrotic lesions, are not readily killed by antibiotics of any kind. Such "resting" organisms, however, may still synthesize toxins and enzymes, such as penicillinase, which may contribute to persistence or extension of the disease. Occasional organisms may survive in tissues under antibiotic treatment sufficient to kill virtually all their fellow organisms. Such "persisters" are not genetically more resistant than the original stock and the reasons for their survival are unknown.[28] It is possible that this phenomenon may play a part in the difficulty of achieving cure in certain cases of staphylococcal infection. Finally biochemical factors difficult to duplicate in vitro may affect the action of antibiotics. Among these may be pH, partial pressure of oxygen, organic compounds, and salt concentrations. For these reasons, although in vitro antibiotic sensitivity tests are of great importance in screening out inefficient antibiotics and suggesting those that may be effective in treatment, the response in an individual case is subject to other factors that make each case almost a new clinical trial.

Treatment must be prompt to minimize permanent valvular damage.

The sensitivity of staphylococci to antibiotics is closely related to the nature of the population from which they are obtained. Representative data are cited in table 3. Staphylococci cultured from persons exposed to the hospital environment, whether from carriers or from infections acquired in the hospital, are highly likely to be resistant to penicillin, streptomycin, and tetracyclines. Resistance to erythromycin may be detected in 15 to 50 per cent of strains, varying to some degree according to the extent of its use. Staphylococci cultured from infections or carriers without obvious contacts with hos-

pitals may be sensitive to penicillin in 50 per cent and to streptomycin and tetracyclines in 7 per cent of cases.

To some extent resistance is a relative term, in that strains classified as resistant may be inhibited by high concentrations of the antibiotic in question. With the possible exception of penicillin, however, toxicity to the patient prevents the uses of other antibiotics in amounts large enough to achieve clinically worthwhile results in infections by resistant strains.

Treatment may be defeated by development of antibiotic resistance by staphylococci. Resistant strains appear readily from spontaneously occurring resistant mutants in patients treated with streptomycin or erythromycin or novobiocin. The emergence of resistant strains may be delayed if each of these agents is given only in combination with another agent, which in the concentration employed, is inhibitory to the staphylococcus. During treatment with penicillin, tetracyclines and, as far as experience goes, with vancomycin, ristocetin, and kanamycin resistant strains rarely, if ever, emerge from sensitive strains. However, where an opportunity exists for contamination of a lesion from external sources, resistant strains of exogenous origin may replace the original sensitive strain.

Choice of Antibiotics

Penicillin is the agent of choice in infections by penicillin-sensitive staphylococci (i.e., staphylococci that produce no penicillinase).[19] These strains are usually inhibited by 0.5 unit of penicillin per milliliter. Recommended treatment is 1 million units of soluble penicillin intramuscularly every 2 to 3 hours for 6 weeks with probenecid 500 mg. orally every 6 hours. Some strains of staphylococci that are both penicillin and streptomycin-sensitive may be killed more rapidly if streptomycin is added; 0.5 Gm. of streptomycin should be given intramuscularly every 6 hours. If signs of vestibular or auditory toxicity appear, the dose should be reduced to 0.5 Gm. every 12 hours.

TABLE 3.—*Antibiotic Sensitivity of* Staphylococcus Aureus *According to Site of Origin*

Antibiotic	Extrahospital strains		Intrahospital strains	
	Carriers*	infections†	Carriers‡	Infections†
	(Per cent of sensitive strains)			
Penicillin	66	49	8	15
Streptomycin	—	87	—	37
Tetracycline	97	78	8	34
Erythromycin	100	99	51	80
Chloramphenicol	100	99	95	99
Novobiocin	97	90	99	95
Bacitracin	—	—	72	92

*Data of Griffith, R. S. et al. Antibiotics Annual, Ed. Welch, H., and Marti-Ibanez, F. New York, Medical Encyclopedia, Inc., 1957-58, p. 370.

†Data of Rogers, D. E.: Staphylococcal Infections. Chicago, Year Book Publishers, 1958, p. 11.

‡Data of Petersdorf, R. G., Curtin, J. A., and Bennett, I. L. Jr.: Arch. Int. Med. **100**: 927, 1957.

The place of penicillin in the treatment of infections by strains of staphylococci moderately or highly resistant to penicillin is subject to differences of opinion. These strains are resistant by virtue of their production of the enzyme penicillinase that inactivates the antibiotic. However, when exposed in small numbers to penicillin they still are killed by concentrations as low as 1 to 2 units per ml. In theory, if these concentrations could be maintained in the immediate vicinity of penicillin-resistant staphylococci for an adequate time, treatment with penicillin should be successful. Whether or not this can be achieved with appreciable frequency in patients is still in doubt. However, several clinical investigators have reported cures of penicillin-resistant staphylococcal endocarditis with very large doses of penicillin, usually in combination with another antibiotic, such as erythromycin.[18, 27, 29] If high-dosage penicillin treatment is considered the treatment of choice, one may give from 50 to 150 million units per day by continuous intravenous drip together with probenecid orally. In addition to penicillin, another antibiotic should be used, either erythromycin, novobiocin, or chloramphenicol, to which the staphylococcus should be sensi-

tive. These agents may be administered initially in doses as high as 0.5 to 1 Gm. intravenously every 6 hours and reduced to half that amount after 3 to 5 days. One million units of penicillin G contain 1.7 mEq. of sodium or potassium. Appropriate amounts of the desired salt should be given where control of salt intake is important.

Vancomycin appears to be the agent of choice for treatment of penicillin-resistant staphylococcal endocarditis, on the basis of admittedly scanty clinical data. This antibiotic is effective against virtually all staphylococci. The bactericidal concentration is not more than twice the bacteriostatic level and readily attained in therapy without significant toxicity. Resistant strains have not been developed by treatment in man nor are they readily obtained in vitro. Toxic manifestations appear to be restricted to occasional pyrogenic reactions, thrombophlebitis, and, rarely, impairment of hearing when high dosage or impaired renal function permit the accumulation of undesirably high blood levels. Geraci and his colleagues have reported bacteriologic cure with vancomycin in 5 of 6 cases of staphylococcal endocarditis.[27] Recommended dosage is 0.5 Gm. intravenously diluted with saline or glucose solution every 4 to 6 hours for 4 to 6 weeks.

Kanamycin, one of the newer antistaphylococcal antibiotics, is related chemically to neomycin, with which it exhibits reciprocal cross-sensitivity and resistance. Bactericidal concentrations are readily attained in the blood after intramuscular injection. Clinical reports are inadequate to evaluate its effectiveness in staphylococcal endocarditis. Careful clinical trial is warranted in staphylococcal infections of the heart in which penicillin or vancomycin is either contraindicated or ineffective. Kanamycin is significantly toxic to the kidneys and the auditory nerve. Damage to these organs may be encountered even on therapeutic dosage, particularly if it is prolonged or if renal disease causes the accumulation of high blood levels. Recommended dosage is 0.5 Gm. intramuscularly 4 to 6 times daily.[30]

Similarly the place of another new antibiotic, ristocetin is still undetermined. It has been reported to have been effective in many staphylococcal infections, including a few cases of endocarditis. However some investigators have found it to be ineffective in some cases of severe systemic staphylococcal infection even without endocarditis.[31] Concentrations that would be bactericidal for staphylococci are higher than can be attained in serum. Marked, but reversible leukopenia and, to a lesser extent, thrombocytopenia have accompanied its use in a variable proportion of patients. Additional evidence is necessary before it can be recommeded for use in staphylococcal endocarditis.

The bacteriostatic antibiotics erythromycin, novobiocin, the tetracyclines, chloramphenicol, and the relatively toxic agents bacitracin and neomycin, for the most part given in various combinations, are not notably effective in staphylococcal endocarditis although occasional cures have been reported. Directions for their use in staphylococcal endocarditis are available and will not be repeated here.[19] It should be noted that recent observations bring into question the advisability of using the common combination of erythromycin and chloramphenicol. Barber has reported, in confirmation of older observations, that staphylococci resistant to erythromycin may concomitantly show partial resistance to chloramphenicol. She recommends erythromycin plus novobiocin as a more desirable combination.[32]

If treatment must be begun on the basis of strong clinical suspicion of staphylococcal endocarditis but before results of blood cultures are available, vancomycin is the preferable agent. A second choice would be penicillin in high dosage plus erythromycin or novobiocin depending on the local pattern of resistance of staphylococci.

As in other serious infections, the use of compounds with glucocorticoid hormonal activity as an adjunct to effective antibiotic therapy has found favor in some quarters. Most students of infectious disease believe that the risks of potentiating the original infec-

tion or of inducing superinfection outweigh the benefits, which appear to be superficial and symptomatic.

The use of anticoagulants in bacterial endocarditis has been abandoned generally.

Criteria of Therapeutic Efficacy

Even with properly selected therapy patients with endocarditis may continue to exhibit fever, embolization, leukocytosis, elevated sedimentation rate, and other signs of infection for several days to weeks. Presumably these signs reflect the period of time necessary to sterilize the lesions and to organize vegetations. These clinical signs are not sufficient indication to change a critically selected course of treatment. The sole urgent indication for change in antibiotics is a persistently positive blood culture. To check this point, blood cultures should be taken repeatedly during early stages of treatment and at any time that the clinical picture becomes worse. Any changes in therapy should be made on the basis of tests to guard against changes in antibiotic sensitivity. If fever, toxicity, and positive blood cultures persist in spite of treatment that should be adequate, localized suppurative complications should be looked for, especially in the kidneys, spleen, bones, lung, and brain.

Results of Treatment

Taken as a whole the results of treatment in recent years of staphylococcal endocarditis have been poor, with the possible exception of the very limited experience with vancomycin. When the staphylococcal endocarditis is a complication of major surgery or advanced systemic disease, especially low recovery rates prevail.[33] Patients who are free of illness other than valvular deformity and who acquire their endocarditis in their home (i.e., nonhospital) environment appear to have a better chance of recovery. This factor may have played a part in the recovery of 8 of a total of 9 patients reported by Melton and Logue.[29] Even in the most apparently favorable case, however, embolism or heart failure from valvular damage inflicted prior to treatment may be unexpectedly fatal. Average recovery rates in larger recent series of patients are about 30 to 50 per cent. No consistent difference in recovery rates is apparent between infections by coagulase-positive and negative strains of staphylococcus.

Prevention

Probably more than 50 per cent of cases of staphylococcal endocarditis are the result of infections acquired in hospitals. Insofar as the rate of hospital-acquired staphylococcal infection can be reduced, the incidence of endocarditis should also decline. Recommendations to this end are numerous and entail many administrative complexities.[34] Among the simpler steps that may be of value are (1) rigorous aseptic technic in surgery, (2) restriction of intravenous catheterization and "cut downs" to the minimum, coupled with careful protection of the site from infection, (3) protection of the inordinately susceptible group of patients by isolation from the general hospital population, (4) meticulous, bacteriologically controlled hospital housekeeping.

Gould has suggested that the high prevalence of penicillin-resistant staphylococci in hospitals is due to the continuous fall-out of penicillin aerosol derived from the widespread use of the antibiotic.[35] If this hypothesis is correct, limitation of contamination of the environment by antibiotics may be an additional step in prevention.

The benefit to be expected from prophylaxis by antibiotics against staphylococcal infection is open to question in view of the high proportion of antibiotic-resistant strains. Where it has been possible to arrange a controlled test of more or less blanket prophylaxis, the results have not disclosed significant benefit. It is possible, however, that prophylaxis against bacterial endocarditis may depend upon the ability to eradicate a small number of infectious organisms from the blood stream or the endocardial surface and hence may be specially feasible. Geraci recommends 1 million units of aqueous procaine penicillin and 1 Gm. of a streptomycin-dihydrostreptomycin mix-

ture 12 hours and again 1 or 2 hours before surgery, dental extraction or endoscopy, with repeated doses for 12 hours to several days afterward. He has not observed endocarditis with this regimen.[27] In contrast, in a controlled study of prophylaxis with chloramphenicol no effect was observed on infections after transurethral prostatectomy.[36] Indeed one patient who received chloramphenicol contracted staphylococcal endocarditis.

Staphylococcal Pericarditis

With the decline in frequency of extensive pneumococcal and streptococcal infections, staphylococci have become the leading cause of acute pyogenic pericarditis. Of 27 cases in patients under 20 years of age occurring between 1937 and 1956, 15 were of staphylococcal etiology.[37]

Staphylococcal pericarditis is usually an incident in severe, bacteremic staphylococcal infection in infants and children. Rarely it appears as a relatively isolated metastatic focus from a mild or inapparent primary infection. Exceptionally it may be a complication of staphylococcal endocarditis.

The clinical manifestions differ in no way from those of acute pyogenic pericarditis due to other organisms; they comprise precordial pain, dyspnea, friction rub, cardiac enlargement, and signs of tamponade. However, symptoms may not be detectable in patients acutely ill with generalized staphylococcal infection. Bacteriologic diagnosis must be established by paracentesis.

The immediate aims of treatment should be the prevention of tamponade by judiciously timed paracentesis and the control of generalized staphylococcal infection by antibiotic treatment along the lines described for endocarditis. Some additional benefit may be obtained by the local instillation of solutions of nonirritating antibiotics, e.g., bacitracin 200 units per ml. or kanamycin 2.5 mg. per ml. at the time of paracentesis. Surgical drainage was formerly considered to be an indispensable element in treatment. Although it is still advocated in all cases by some authorities, current experience suggests that some patients may be cured by antibiotic treatment alone. If the effusion recurs or evidence of infection persists under treatment, surgical drainage is indicated.

The results of treatment of staphylococcal pericarditis are determined in large measure by the response of the serious infections with which it is associated. The mortality in a series of patients treated with penicillin between 1944 and 1956 was close to 50 per cent.[37]

There are indications that healed staphylococcal pericarditis may produce the syndrome of constrictive pericarditis. Rigorous proof, however, is still wanting.[38]

Staphylococcal Myocarditis

In fatal cases of uncontrolled staphylococcal bacteremia the myocardium is usually peppered with miliary abscesses ranging from microscopic to grossly visible size. Whether they produce clinical signs or symptoms is unknown. In line with the suggestion made for the milder myocardial lesions of subacute bacterial endocarditis, they may contribute to the vascular collapse that often accompanies staphylococcal bacteremia.[39]

Solitary abscess of the myocardium is exceedingly rare. Among 7 cases reviewed by Weiss and Wilkins, at least 1 was caused by *Staphylococcus aureus*.[39] The primary site from which the myocardial lesion arises is rarely apparent. The abscess is unaccompanied by signs of infection and manifests itself for the first time when it ruptures into the pericardium. In the few reported cases, the symptoms have been sudden precordial pain followed by signs of tamponade and death from hemopericardium within a few hours.

Summary

The basic problems of staphylococcal infections do not seem near to solution. Possibly an effective and safe antibiotic will be found to which resistant, pathogenic staphylococcal mutants will not appear. This may not be an overly sanguine hope. Had it not been for the ability of the staphylococcus to synthesize

penicillinase, this goal would have been achieved already, for staphylococcal mutants pathogenic to man and intrinsically resistant to penicillin (i.e., without the production of penicillinase) have not been reported. Even with better antibiotics grave problems would remain, however, for the staphylococcus often inflicts severe or even irremediable damage, especially in the heart, before the disease can be diagnosed.

Prevention is the crucial problem. Refinements in isolation technics and hospital sanitation may improve the protection of the patient in the operating room and the newborn infant in the nursery. Nevertheless, the hard core of infections in debilitated or otherwise susceptible medical patients will probably remain. To help them it will be necessary to learn to restore the mechanisms of normal host resistance that have been depleted by disease.

SUMMARIO IN INTERLINGUA

Il non pare que le solution del problemas fundamental de infectiones staphylococcal es imminente. Il es possible que un efficace e innocente antibiotico va esser trovate sin que mutantes resistente del staphylococcos pathogene va disveloppar se contra illo. Iste spero es forsan non troppo promittente. Si le staphylococcos non habeva le capacitate de synthetisar penicillinase, ille objectivo esserea jam attingite, proque mutantes staphylococcal que es pathogene pro humanos e que possede un resistentia intrinsee contra penicillina—i.e. un resistentia non dependente del production de penicillinase—ha non ancora essite reportate. Tamen, mesmo si melior antibioticos esseva cognoscite, grave problemas remanerea, proque le staphylococcos inflige frequentemente haver o mesmo irreparabile injurias, specialmente in le caso del corde, ante que le morbo pote esser diagnosticate.

Le problema critic es le prevention. Le affinamento del technicas de isolation e del sanitation hospitalari va possibilemente meliorar le protection del patiente in le sala de operation e le neonato in le nursery. Nonobstante, un residuo irreducibile de infectiones in debilitate o alteremente susceptibile patientes medical va probabilemente permaner. Pro adjuvar tal patientes, il va esser necessari trovar methodos pro restaurar le mechanismos del normal resistentia del organismo le quales ha essite deteriorate per le processo pathologic.

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CLINICAL PROGRESS

Fats, Cholesterol, and Coronary Heart Disease

A Review of Recent Progress

By NORMAN JOLLIFFE, M.D.

WHAT dietary advice can the medical profession now give to patients who ask, "What can I do to help avoid coronary heart disease?" Agreed to by almost all medical authorities is, "Never become overweight, and if overweight reduce and stay reduced."[1] Also agreed to, but less unanimously[2] is the additional admonition "If the family history includes early deaths from atherosclerosis or, if the blood cholesterol is above average, the patient would also be well advised to restrict his fat intake to not more than 25 or 30 per cent of the total calories." To this medical consensus, I have additionally recommended that a significant portion of this dietary fat be derived from the predominantly unsaturated fats and oils, and extend the coverage to all men of voting age and to all women after their 40's.[3]

What findings within recent years have been so significant as to change our thinking on atherosclerosis from "one of hopelessness to one of hopefulness," from "Does diet have anything to do with atherosclerosis?" or, more specifically, "Does fat have anything to do with atherosclerosis?" to "What type of fat is involved?" "How great is the effect?" and "What is the mechanism of their action?" Finally, "How can these factors be applied in practical dietetics and to public health practices?"

Although all major discoveries have their foundations in the more distant past, (and this one is not an exception), the immediate break-through was started by Kinsell et al.[4] in 1952, who showed that the ingestion of certain different vegetable oils under the rigidly controlled conditions of a metabolism ward was followed by a major fall in plasma cholesterol and phospholipid levels. This finding was soon confirmed by several laboratories[5–10] but not all vegetable oils possessed this cholesterol-lowering property and not all animal fats and oils raised cholesterols. At this point Bronte-Stewart, Antonis, Eales, and Brock[10] clearly showed that certain marine and vegetable oils which, in their natural state, lowered the elevated serum cholesterol level in man, after hydrogenation acted to elevate it just as do certain naturally occurring highly saturated fats, e.g., those derived from coconuts and cow's milk. This discovery, now confirmed in other laboratories[11, 12] has clearly proved to be of fundamental importance, like the finding of an important piece in a complicated jigsaw puzzle. The entire puzzle in all its details is not yet clear because many pieces have not yet been found, but the broad outline and framework are now evident and are of firmness sufficient to base broad dietetic recommendations. In this respect it is of utmost importance to determine whether or not people in their usual environment can be induced by public health methods to modify their diet over a long period of time so that their blood lipids, as measured by the cholesterol-lipoprotein system, will be favorably influenced. Then, and possibly only then, can one obtain sufficiently large groups of test subjects to determine directly whether or not this dietary change is followed by a favorable

From the Bureau of Nutrition and the Diet and Coronary Heart Disease Study Project, Department of Health, City of New York, N. Y.

TABLE 1.—*Prevalence of Aortic Arteriosclerosis in the Bantu (After Laurie and Woods[15])*

Age group	Sex	Per cent clear	Per cent stage 1	Per cent stage 2	Per cent stage 3	Per cent stage 4	Number of subjects
20-29	M	26	35	26	4	9	23
	F	28	50	22	—	—	18
30-39	M	25	46	8	4	17	24
	F	32	32	30	—	6	34
40-49	M	19	25	33	17	6	36
	F	15	25	30	30	—	20
50-59	M	14	41	21	8	16	37
	F	5	16	11	52	16	19
60-69	M	—	18	27	30	25	40
	F	—	11	21	31	37	19
70 plus	M	—	—	53	29	18	17
	F	—	—	—	77	23	13
Number of subjects		44	80	73	56	47	300
Per cent of subjects		14.7	26.6	24.3	18.7	15.7	100

influence on deaths from atherosclerosis, particularly in men under age 65.

Prevalence of Coronary Heart Disease

To appreciate fully the significance of the recent developments in our basic knowledge of fat metabolism, it is necessary to review briefly the background information regarding fats, cholesterol, and atherosclerosis. Coronary atherosclerosis is recognized by most investigators as the keystone, the *sine qua non* of the problem of coronary heart disease.[13] It is also true, but not so well recognized, that the differences in prevalence of coronary heart disease in various populations do not exactly parallel the degree or extent of atherosclerosis. For example Becker[14] did find aortic atherosclerosis at autopsy common among the Bantu, a finding concurred in by Laurie and Woods.[15] Their over-all findings are shown in table 1. However, it is important to note that although aortic atherosclerosis is common in the Bantu, coronary heart disease as a cause of death is a rarity while cerebral vascular complications are not much different from those in European populations. Some other factor, or factors must also be present to determine which of several individuals with approximately equal amounts of coronary atherosclerosis are going to develop clinical coronary heart disease. Among the additional factors thought to play a role are the chance strategic location of the atherosclerosis plaques, anatomic variations of the coronary artery vessels, and abnormal intravascular clotting. This last item includes increased blood coagulability and "sludging," decreased fibrinolysis, and changes in such other factors as lipid clearing and capillary fragility. Nevertheless, when coronary atherosclerosis can be largely prevented, delayed, or postponed, or when these additional factors have been largely controlled, life expectancy at age 50 may be significantly lengthened.

Coronary artery disease was a rarity in mortality statistics prior to 1920. It has now become our no.-1 cause of death in middle age as well as after 65. Much of this reported increase unquestionably is factitious[16, 17] resulting from increased medical awareness, fashions in medical diagnosis, better diagnostic methods and their wider use, as well as from changes in reporting. There remains, however, according to Lew, a 15 per cent increase between 1940 and 1955 that cannot be accounted for by these factitious factors. Although this increase seems to some to be insignificant, it amounts to 1 per cent per year since 1940, at which time much of the reported increase had already occurred. By 1940, both awareness and clinical diagnostic facilities had been largely developed and disseminated throughout the entire medical profession. This increase in reported death rates has been especially significant among younger and middle-age males. The *Lancet* editorially states . . . "All cardiologists whose experience goes back 30 years or more seem to agree with the vital statisticians that the higher mortality rates reflect a real increase in coronary artery disease, and also that young people . . . are now affected more often than formerly."[18]

Important evidence that coronary heart disease has actually increased in middle age and after is the fact that life expectancy at

age 50 has not materially increased since 1900.[19] For example, in 1900, life expectancy in the United States at age 50 was about 20.8 years while in 1950 it had increased but 2.2 years to about 23 years. This relatively small increase, 10.6 per cent, has occurred in spite of the conquering of pneumonia and many other acute infections during middle life, the saving of lives due to increased skill in surgery, the marked reduction in deaths from syphilitic heart disease, bacterial endocarditis, rheumatic heart disease, and tuberculosis.

The mortality from coronary heart disease is high in all the western industrialized countries of the world. But among them the ratio between the highest and the lowest may be as much as 4 to 1 and, between Japan and the United States, it is as high as 8 to 10 to 1[20] (table 2).

It is highest in the United States, Canada, Australia, New Zealand, and Finland but there are national, cultural, and ethnic groups in which such increases have not been observed and among whom the mortality from coronary heart disease is from one fourth to one tenth or even less of that in this country.[21] Examples are the Japanese,[22] the Bantu in the Union of South Africa,[23] Guatemalan Indians,[24] Nigerians,[25] Yemenite Jews in Israel,[26] Italians and Sardinians in Italy,[27] and low-income men in Madrid.[28] These mortality rates must be critically examined, for there are differences in awareness, fashions in diagnosis, and differences in reporting, as well as true differences in the actual disease rate. Ordinarily, differences in reported rates of less than 1-fold between countries should, in most instances, be discounted, and in the absence of strong supporting data, be attributed to factitious differences. On the other hand, major differences of the order of 2, 4, or 10 to 1, or even greater cannot with prudence be ignored when there are means available for checking their rough accuracy. Ad hoc surveys[22, 27, 29-31] have done much to support the rough accuracy of these statistical figures. These teams of competent observers failed to find a prevalence of coronary heart disease comparable in any way to that found in this country. As pointed out by Keys,[21] it is not reasonable to suppose that in these places, only the patients with coronary heart disease stay away from doctors, hospital clinics, and the autopsy table, when patients with other diseases—cancer, cirrhosis of the liver, nephritis, cerebral vascular lesions, valvular heart disease, and so on—do appear and with a frequency approximately equal to that in the western civilized countries.

Vital statistics are often censured for their unreliability because of the considerable discrepancy in individual cases between the cause of death given on the death certificate and the actual one found at autopsy. This condition undoubtedly exists, but the final data based on the death certificates are approximately correct due to a balancing of errors. For

TABLE 2.—*Death Rates from ISC Categories B-26 and 420, 1954 (From WHO[20])*

Country	Death rate ISC category B-26*	420
United States	704.7	660
Australia	577.4	516
Austria	293.9	
Belgium	250.1	
Canada	588.3	550
Ceylon	103.4	
Chile	267.3	
Denmark	294.8	260
Finland	621.7	483
France	109.9	106
German Fed.	313.7	194
Italy	226.8	120
Japan	122.5	50
New Zealand	525.7	492
Norway	248.8	210
Portugal	107.7	
Sweden	294.6	216
Switzerland	273.0	173
United Kingdom	427.5	371
Yugoslavia	68.2	

*ISC Category B-26 includes 420—arteriosclerotic heart disease, 421—chronic endocarditis, 422—other degeneration of the heart.

example, in a comparison of autopsy findings with the original death certificates in 1,889 subjects in 12 upper New York State hospitals in 1951 and 1952 there was full agreement in only 72.8 per cent of 276 deaths originally certified as due to "arteriosclerotic heart disease."[32] This does not mean that the mortality rate from ischemic heart disease was overestimated by the original death certificates because autopsies disclosed 66 additional deaths from this disease that had been originally attributed to other causes in the death certificate; the final result was that the rate reported by the death certificates was 96.7 per cent correct.[21]

In addition to the statistical data and the ad hoc field survey findings, other data support this contention that the prevalence of clinical coronary heart disease varies markedly in different groups. Clinicians with wide international and interracial experience long have held that at equal age, there are wide variations between countries,[18, 33] between races in the same countries,[23] as well as between different socioeconomic groups in the same country.[23] Necropsy studies support these differences.[32, 34, 35] Thus it can be concluded that there are marked differences between countries and between communities in the age-specific mortality rates for coronary heart disease.

Environmental Factors

This increase in the prevalence of clinical coronary heart disease in some populations and the lack of observed changes in others indict environment as a significant cause even though heredity and genetic factors may determine the degree of susceptibility.[21, 27] Among the environmental factors that have been considered are luxury living, stress, differences in physical activity, tobacco, and diet. Diet includes deficiencies, extra calories and the resulting obesity, protein intake, excess fat, and differences in fat quality.

"Luxury living," "high standard of living," and "prosperity" are medically meaningless terms. One must find and designate more clearly the responsible factor or factors in these broad terms. Certainly, all aspects of "poverty," "low standard of living," and "depression" cannot be beneficial. Besides, who would be so naive as to recommend this as therapy for our coronary patients or as a public health measure to help prevent coronary heart disease!

Stress

Stress is a factor to be considered, particularly the type of stress related to western civilization, urbanization, and prosperity. Old-fashioned stress such as the stress of obtaining food to keep alive, the stress of "the jungle," the stress of mating or to obtain and keep a desirable mate, the frustrations of parenthood, and the noises of community living have certainly been with mankind ever since he developed a communal life. It is doubtful whether at any previous period of mankind these factors of old-fashioned stress have ever been less than at present. But the types of stress related to that of masses of people mobile upward economically with most persons feeling a bounden duty to elevate themselves and their children to a higher economic and social group, the stress of failing to escape from the boom, chatter, and jangle of television, radio, and the telephone—all may represent a newer type of stress to which mankind is making but poor adjustment. Studies showing differences between personality and emotional make-up of people having coronary heart disease and healthy controls have all been done retrospectively. No prospective study along this line has been reported. This type of study should be done.

Rosenman and Friedman[36] have recently attempted to measure the effects of this type of stress on a group of 42 volunteer male accountants. This group was selected because of the unusual phasic variations of their work and its associated deadline. Serum cholesterols and blood clotting times were determined bimonthly and, in 83 per cent of the subjects, the maximum cholesterol concentrations occurred at the time of the maximum

stress as measured by nearness to income tax deadlines. Blood clotting time was shortened from an average of 9.4 minutes during minimal stress to 5 minutes at the time of maximum stress. The authors could not ascribe the changes in either cholesterol or blood clotting patterns to diet or to changes in weight. The subjects were free-living accountants noted for "snacks" at maximum work periods. These snacks, usually containing large amounts of saturated fats, could account for the failure to lose weight at maximum work periods, as well as the changes in blood cholesterol and clotting time. Also, all these subjects were on an ad libitum high-fat diet under which condition considerable fluctuations in blood cholesterol levels may occur. It remains to be proved whether or not this type of stress during a constant diet actually does influence the blood lipid levels.*

Old-fashioned stress and strain were certainly greater in England and Norway than in the United States during the World War of 1939-45. Yet, there is no sudden separation in the graphs of the mortality rates from coronary heart disease in England and in the United States during the war years to reflect the effect of stress and strain, particularly during the Battle of Britain. There is evidence that in Norway during the German occupation there was a significant decrease in mortality rates attributed to coronary heart disease.[37] One can conclude from this data that stress is not a major factor in coronary heart disease.

Exercise

Regular physical activity undoubtedly plays an important role in maintaining cardiovascular efficiency, physical fitness, and a trim figure. But it cannot explain major differences in mortality statistics, otherwise the long-walking, bicycle-riding, exercise-loving Englishman should have a coronary heart disease rate more comparable to that of the Italian than to the little-walking, car-riding, physically indolent American. A cooperative study by physicians in Minnesota, Italy, Sweden, Spain, and South Africa[38] finds that differences in serum cholesterol, and, by inference the coronary heart disease rate, were associated with different dietary fat intakes rather than differences in physical activity. However, as pointed out by Mann and his co-workers,[39] physical activity can prevent the rise in blood cholesterol associated with an increased saturated fat intake provided the physical exertion is sufficient to prevent weight gain. At this point it is well to note that Gordon, Lewis, Eales, and Brock[40] have demonstrated falling total blood cholesterol levels during periods of weight gain when the increase in calories was derived from sunflower seed oil.

It still remains problematic whether regular physical exertion produces its beneficial result by decreasing the blood cholesterol level or by increasing collateral circulation and circulatory efficiency. Both factors may play a role.

Tobacco

Excessive cigarette smoking has been indicated as a factor in coronary heart disease. According to Hammond,[41] a high association exists between cigarette smoking and the incidence of coronary artery disease. The death rate from this cause was 75 per cent higher among cigarette smokers than for a comparable group of men who had never smoked. Moreover, death rates due to coronary artery disease increased with the amount of cigarette smoking. One may speculate that this could operate either through the vasospastic action of cigarette smoking on a previously damaged coronary vessel or it may well be associated with increased saturated fat consumption accompanying oral compulsion. Persons who smoke 2 or more packs of cigarettes a day

*Since this paper was submitted for publication, Friedman and Rosenman have recently extended these observations by selecting their subjects according to degrees of stress and found higher serum cholesterol levels in the subjects most stressed as measured by their criteria. (Friedman, M., and Rosenman, R. H.: Association of specific overt behavior pattern with blood and cardiovascular findings. J.A.M.A. 169: 1286, 1959.)

may, in general, be those who also eat an unusual amount of saturated fat. This possible association may be a fruitful field for study.

Climate

There is no good evidence that climate is an important factor. The difficulty lies in that climate influences so many characteristics that even approximate comparability is almost impossible. However, some inference may be drawn from data for individual states in the United States.[43] Florida and Maine have age-adjusted death rates of coronary heart disease in the same quartile (as well as other similar characteristics) and yet their climates are certainly different. On the other hand, adjoining states such as West Virginia and Maryland, or Mississippi and Louisiana, have essentially the same climate, yet the first of each pair has age-adjusted coronary heart disease rates in the lowest quartile whereas the second is in the highest quartile.

Diet and Coronary Heart Disease

Specific dietary deficiencies other than pyridoxine, certain amino acids, and essential fatty acids have not been related to coronary heart disease. As a matter of fact, differences in protein quantity varying from 11 to 20 per cent of total daily calories with calories and fat quality and quantity remaining constant has not resulted in significant alteration of the blood lipids.[44] Olsen[45] has demonstrated in 9 subjects that, with calories, fat quantity, and fat quality remaining constant, a reduction of protein from 100 Gm. daily to 25 Gm. daily resulted in a fall in blood cholesterol within 2 weeks. Twenty-five grams of total protein is within the range of protein inadequacy; this is not therefore within the range of either a practical or adequate human dietary regime. These observations do not prove that protein quantity or quality do not play a role in coronary heart disease. It is to be noted, however, that all other experimental factors producing atherosclerosis in the laboratory animal were always associated with changes in blood lipids. Protein per se, therefore, within the range of most adequate human dietaries holds little promise of being a significant factor in atherosclerosis.

Pyridoxine deficiency is now thought to operate through a disturbance in fat metabolism, resulting from failure to convert linoleic acid to arachidonic acid.

Although nicotinic acid has been shown to lower the blood cholesterol, the dose employed has been so large that the effects are pharmacologic rather than nutritive. Altschul and his colleagues[46] reported that 1 to 4 Gm. of nicotinic acid ingested in a 24-hour period successfully reduced serum cholesterol levels in normal and hypercholesterolemic persons. Long-term effects of large daily doses of nicotinic acid in patients with hypercholesterolemia were subsequently observed by Parsons and others.[47, 48] They showed that significant reductions in the blood cholesterol and total lipids could be obtained in these persons with this therapy and maintained for periods up to 1½ years as long as therapy continued. Moreover, Parsons was able to show that this effect could not be obtained by the use of nicotinamide, rather than nicotinic acid.[49]

These studies were conducted with no change in the subjects' previous diet. Presumably, then, all changes in cholesterol level could be attributed entirely to the use of nicotinic acid.

The exact mechanism that enables nicotinic acid to produce the observed changes in the blood lipids is not yet clear. However, the failure of nicotinamide to produce similar results, and the large doses of niacin required, indicate that the effects of niacin are pharmacologic.

Obesity is also an important factor. It is associated, particularly in middle age[50] with significantly higher mortality rates than in normal-weight subjects of comparable age and sex. Obesity possibly operates, in addition to a greater work load upon the circulatory system, by the obese subject's consuming greater amounts of fat calories of the wrong quality and of saturated fat precursors than do their trim counterparts. But important as

obesity is, it has been pointed out by Keys that obesity in itself cannot explain differences of several-fold between countries, and he further observes that if obesity were eliminated in the United States, coronary heart disease would still be its no.-1 public health problem.

Fat Consumption and Coronary Heart Disease Association

The dietary factors that correlate best with reported international mortality rates of coronary heart disease are those associated with the fat and protein available for human consumption in national dietaries. These latter figures measure the food that enters into retail outlets. Much has been made of the fact[51] that food balance figures are not a good index of actual fat consumption because of the considerable waste that exists between receipt by the retail store and disappearance from the plate. Indeed, there is much waste between the retail store and the mouth but that waste is not confined to one class of foods. As a matter of fact, there is even a possible higher waste at the retail stores of fresh fruits and vegetables than of fat, proportionately little of which is wasted at the retail level. From the market basket to the plate, the trimming and discarding of fats and the peeling, waste and spoilage of fruits, vegetables, and breads are proportionately not far different. The same is probably true for plate waste. Therefore, the 148 Gm. of fat that entered into retail sales in 1956 include much fat that is wasted; likewise there was an equal or greater waste of bread, fruits, and vegetables. Thus, the percentage composition of our calories derived from fat, carbohydrate, and protein at the retail level probably reasonably approximates that actually consumed. Support for this conclusion is the fact that dietary surveys indicate, almost without exception, that the approximate percentage composition of the diet as eaten *agrees* with the percentage contribution of food disappearance. Great significance can therefore be given to the figures on table 3 showing the percentage increase in fat calories in our national food supply since 1910. It has increased from 32.2 per cent in 1910 to over 41 per cent in 1955.

TABLE 3.—*Fat Calories as a Percentage of the Total Calories Per Capita Available for Consumption in the United States in Selected Years. (After USDA[52])*

Year	Per cent
1910	32.2
1920	33.5
1930	35.0
1940	38.3
1950	40.1
1955	41.4

The first correlation between fat consumption and international death rates of coronary heart disease was made by Keys and his associates.[53] As expressed in Keys and White[54] this relationship between the total fat intake and coronary heart disease rates for males below 65 may be expressed as follows: Populations with fat intakes approximating 40 per cent of the total calories have high death rates; populations with total fat intakes below 20 per cent of total calories have low death rates; populations with intermediate fat intakes have intermediate death rates. This correlation between total fat and death rates of coronary heart disease was soon challenged by the National Dairy Council[55] and later, among others, by Yerushalmy and Hilleboe,[56] Page, Pollack et al.,[51] Yudkin,[57] and Mann.[58] It was pointed out by the National Dairy Council Digest[55] that, in Norway, Sweden, and Denmark, the percentage of total calories derived from either total fat or from animal fat is comparable with that of the United States or the United Kingdom, while death rates from heart disease at all ages or in the age groups of 50 to 54 years are only about one third of those in the United States. The National Dairy Council, however, did not distinguish between fats derived from marine animals, which are of the unsaturated type, and from land animals, which are predominantly saturated. At that time, however, the differences in quality of these fats were not generally appreciated. In the low coronary death rate-high fat intake countries (Sweden

TABLE 4.—*Rank Correlation Coefficients* between Various Dietary Components and Death Rates from Arteriosclerotic and Degenerative Heart Disease (B-26) in 22 Countries*†

	Absolute value	Per cent of total calories
Total calories	0.723	——
Calories from fat	0.659	0.587
Animal fat‡	0.684	0.677
Vegetable fat‡	−0.236	−0.468
Calories from protein	0.709	0.172
Animal protein	0.756	0.643
Vegetable protein	−0.430	−0.651

*Critical values of r for $\alpha = 0.05$ and $\alpha = 0.02$, when N is 21, are $\pm$ 0.438 and $\pm$ 0.531; when N is 22 they are $\pm$ 0.428 and $\pm$ 0.508.

†Above data taken from table 3 of Yerushalmy and Hilleboe.[56]

‡For 21 countries, data not available for France.

Norway, Denmark) the consumption of both fish and marine oils is large—several times that of the United States. In addition, the consumption of unhydrogenated vegetable fats is larger.

Following the National Dairy Council, Yerushalmy and Hilleboe[56] were the next to question seriously the total fat concept. They considered that "the dietary fat-heart disease association is *not* unique or specific since the association between *fat* and heart disease mortality is not so strong as that between *animal protein* and heart disease." Yerushalmy and Hilleboe additionally criticized certain previous work on the association between dietary fat and mortality rates as failing "to probe further, to go beyond the simple, apparent association and to investigate related variables." However, like the National Dairy Council, Yerushalmy and Hilleboe considered all fat as equal in quality and developed their paper only on the information available in November 1955. They made correlations between several dietary constituents and death rates from coronary heart disease (B-26) and found even better rank correlations (table 4) with total calories, animal fat, and animal protein than with total fat. Yerushalmy and Hilleboe did not point out that in low-calorie countries (less than 2,700 calories) the total fat consumption was generally low and usually paralleled or varied with the total calories. Where consumption of animal protein is high (more than 5 per cent of calories), the total fat intake was also high (more than 30 per cent of calories). In both instances, as pointed out by Jolliffe and Archer,[60] the dietary fat accompanying these 2 factors accounted for *practically all* of their associations. Thus, according to Yerushalmy and Hilleboe's criterion of "valid" association, the saturated-type fat-coronary heart disease association is valid and accounts for *almost 70 per cent* of the variation in B-26 death rates in the 20 countries examined (table 5). When international food consumption figures are tabulated so as to obtain more accurate data of fat quality, a more definite answer may be obtained.

Yudkin[57] in an extensive analysis of environmental factors associated with death rates of coronary heart disease made the observation that " . . . one begins to have the uneasy feeling that both the proponents and the opponents of a dietary hypothesis are quoting only those which support their view." He then correlated many environmental factors with the death rates of coronary heart disease. Like the National Dairy Council[55] and Yerushalmy and Hilleboe,[56] he showed that total fat-coronary heart disease association was not so high as that with calories and animal fats. He also showed that vegetable fats alone or hydrogenated fats alone did not correlate any better than total fat. He also observed that there seems to be a threshold level of total fats (about 30 to 35 per cent of calories or around 120 Gm. of fat) above which coronary heart disease was common, while below this level it was uncommon. Yudkin also made the observation that, over the years in the United Kingdom, the best correlation of all was with the number of registered radio and television sets, indicating that a non-sequitur must be validated by methods other than statistical association.

The paper by Page, Stare, Corcoran, Pol-

lack, and Wilkinson[51] is a report *to* the American Heart Association and *to* the American Society for the Study of Arteriosclerosis (rather than from either of these organizations). The body of the report is a critical and sobering review of the literature up to early 1957 on the epidemiologic factors of coronary heart disease. Their conclusions however, are as follows (italics mine):

Atherosclerosis, cerebral thrombosis, and myocardial infarction are diseases in which numerous factors are involved. Diet and nutrition are important factors in experimental atherosclerosis and, very probably, in the human disease. Thrombosis and infarction of the cerebral, cardiac, and renal vessels occur in severely sclerosed arteries, but so far neither has been clearly produced experimentally.

Evidence is presented to suggest a possible general association with high fat consumption, but it is difficult to disentangle this from caloric balance, exercise, changes in body weight, and other metabolic and dietary factors that may be involved. *Thus the evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral artery disease.* On the other hand, the fact that obesity is a nutritional failure, that it is caused by consuming more energy than one expends, that the dietary fats are the most concentrated source of energy, providing some 40 to 45 per cent of the daily calorie intake, suggests that many should consume less calories. For most, this will mean eating less fat.

Prudence, as well as habit and taste will dictate the selection of a diet with some fat. Diets providing 25 to 30 per cent of the calories from fat, rather than the current 40 to 45 per cent in the American diet can still provide palatable meals for our accustomed tastes.

The key points of nutritional common sense for better health generally, and most likely in regard to atherosclerosis specifically, consist of a balanced, varied diet that adjusts total calories to reach or maintain a desirable weight. Such a diet should provide more protein from lean meat, fish, poultry and animal products, and a reasonable selection of fruits and vegetables. *The fat content should be sufficient only to meet calorie and essential fatty acid demands.*

These conclusions obviously apply to the general population, and not to patients, or to individuals with a strong family history of early deaths from cardiovascular disease, who are being observed with some regularity by their physicians. Here, the newer concepts of nutrition readily suggest various types of diet therapy that may prove useful in certain patients. Investigative procedures of this type, together with continued basic research, will, in time, provide the facts upon which sound dietary recommendations may be made to the public at large and which may help in lessening the prevalence of cerebral and coronary heart disease with consequent stroke and myocardial infarction.

It is recognized that this is a joint paper and that it was written to satisfy all 5 contributors. Nevertheless, it is difficult to reconcile the 3 recommendations in italicized type

TABLE 5.—*Death Rates for Category B-26 and Various Dietary Factors**

Country	Date rate†	Total available daily calories	Total fat intake as a per cent of total calories	Saturated types of fat intake as per cent of total calories	Animal protein intake as per cent of total calories
United States	704.7	3070	39.2	33.5	8.2
Australia	577.4	3160	37.9	34.7	7.3
Austria	293.9	2820	31.3	23.9	5.8
Belgium	250.1	2980	35.0	24.4	5.7
Canada	588.3	3130	38.0	35.0	8.0
Ceylon	103.4	1980	15.2	11.8	2.2
Chile	267.3	2490	19.8	12.0	4.3
Denmark	294.8	3370	38.3	25.5	6.1
Finland	621.7	3170	31.1	28.4	6.8
France	109.9	2850	29.5	20.7	6.4
German Fed.	313.7	2950	35.6	23.0	5.6
Italy	226.8	2550	22.3	10.5	3.6
Japan	122.5	2005	7.9	1.4	2.6
New Zealand	525.7	3370	39.8	37.6	8.2
Norway	248.8	3130	38.0	17.0	6.4
Portugal	107.7	2560	24.5	9.4	3.9
Sweden	294.6	3070	39.4	28.3	7.3
Switzerland	273.0	3100	33.6	23.6	6.6
United Kingdom	427.5	3270	38.4	35.0	5.9
Yugoslavia	68.2	2525	19.1	13.2	2.8

*Data derived from.[85]

†Death rates for Category B-26 (ISC) per 100,000 males, aged 55-59. Values actually used in the correlations were the logarithms of the numbers in this column. WHO[20]

above. The first recommends no drastic change, which, in many instances, has been interpreted as no change at all, the second a moderate decrease in fat from 40-45 per cent to 25-30 per cent of the calories, while the third suggests only enough fat to meet essential fatty acid and calorie needs.

Mann[58] in his review of the epidemiologic data, along with Yerushalmy and Hilleboe and Page et al., questions the validity of these data. This point has been dealt with at length previously by Keys[61] and reviewed by Jolliffe.[3] As previously mentioned it is recognized by all that methods of recording, reporting, and degrees of medical sophistication may well account for differences of 100 per cent between countries of similar technologic development. But differences in age-specific coronary heart disease rates between countries and communities of 200 to 1,000 per cent, when other methods such as the ad hoc surveys of Keys and his associates exist to check the rough accuracy of these vital statistics, *cannot* with prudence be ignored.

Examination of some of Yudkin's tables yields some information on this point. For example, in the United Kingdom, Denmark, Sweden, and Norway, where technologic development and medical sophistication are high and approximately similar, the reported death rates in 1952 from coronary heart disease for men aged 55 to 64 varies from 239 in Norway to 470 in the United Kingdom. Certainly no prudent individual would consider that the physicians in Norway are assigning some other causes of death to more than half of their cases of coronary heart disease, or, as an alternative, that physicians in the United Kingdom are labeling with coronary disease more than half of the patients who do not have it at all.

In addition to the statistical data noted above, other supporting evidence is the experience of clinicians that the prevalence of coronary heart disease does, in fact, vary markedly in different groups.

Changes in Fat Quality

In addition to a 29-per cent increase (9 percentile points) in the past 45 years in the percentage of total calories derived from fat available in our national food supply (table 3), the accompanying change in fat quality may be of even greater significance. Historically, a nation's increased prosperity is quite regularly accompanied by an increased consumption of fats of the saturated type (meat, milk, and eggs) at the expense of fats from unsaturated sources (from fish, grain, nuts, and vegetables) and of carbohydrates from grain and tubers. This change in fat quality regularly accompanies an increase in the western standard of living. In addition, the greater the marbling of the meat and the richer the milk, the greater is their prestige value. Meat, milk, and dairy products have become prestige foods largely because: (1) they are universally liked and easy to prepare; (2) they are more expensive, therefore desirable, when compared to the leaner products; and finally (3) through clever advertising and promotion operating in a milieu of regulatory legislation favoring these products the modern housewife is made to feel guilty unless she serves her family more marbled meat and fat dairy products than are called for by a nutritious and well-balanced diet. For example, the 31 ounces of milk products, in terms of fluid whole milk, consumed per capita daily in the United States[52] is almost double the desirable goal of 16 ounces recommended for most countries.

When a person consumes any item of food in excess of energy and nutritional needs, he is faced with 2 possibilities: (1) continue the excess amount of that particular food but cut down on other foods, and thus risk a deficiency disease; or (2) continue to eat sufficient amounts of other food for nutritional need and thus become obese.

The other major factor contributing to the change in fat quality is "hydrogenation," a process by which oils such as cotton seed or soy bean are changed into solid fats. As commonly carried out in this country, hydrogena-

tion produces 4 types of chemical change, according to the Committee on Fats in Human Nutrition of the Food and Nutrition Board:[62]

1. Hydrogen is added at double bonds, producing saturated from unsaturated fatty acids or stepwise decreasing the number of double bonds in polyunsaturated acids as indicated by a lowering of the iodine number. The melting point is raised.

2. The double bond may shift position along the carbon chain, producing iso-acid forms. These new unsaturated acids may have the same iodine number but may differ from the original in melting point.

3. The predominantly occurring *cis* configuration may change to the *trans* configuration. This isomerization also leaves the iodine number unchanged but leads to a significant rise in the melting point. For example, oleic acid melts at 13° C. and is liquid; its trans isomer melts at 44° C. and thus is solid at room temperature.

4. With linoleic, linolenic, or arachidonic acids there may be conjugation, in which system the double bonds are not separated by a methylene group. These conjugated systems are relatively rare in natural food fats.

The net result of all these changes is a fat solid at ordinary room temperature with an iodine value about that of olive oil. The linoleic acid content has been reduced from around 50 per cent originally to 3 to 8 per cent after hydrogenation.

Brown[63] has estimated that hydrogenation of cotton seed oil and soy bean oil alone destroys over 1 billion pounds of linoleic acid annually which, it may be calculated, amounts to about 8 Gm. per person per day. Since, according to McCann and Trulson,[64] our total daily intake of linoleic acid is 9.7 Gm. per person per day (2.7 per cent of the 3,220 calories per day total diet shown), these 8 grams destroyed, if added to the diet, would almost double the linoleic acid content and bring it up to almost 5 per cent. Thus, a significant loss of an essential nutrient has occurred, especially if the requirement for linoleic acid is proportional to the intake of saturated fat or if the minimum requirement is somewhere between 5 and 10 per cent of our calories.

As shown by Kinsell et al.,[65] 10 per cent of the diet as linoleic acid in short range, metabolic ward experiments will result in a fall in blood cholesterol and phospholipids in the majority of the age group of 20 to 29 years. This may indicate that the requirement for linoleic acid in this age is somewhat less than 10 per cent of the daily calories.

The nutritional effects of the isomers formed during hydrogenation have been extensively studied[66] and, in terms of growth, maturation, and reproduction, such fats are equivalent to their precursors. Since trans-acids do not replace cis-acids[67, 68] in remedying essential fatty acid deficiencies, it seems probable that some of these isomers formed by hydrogenation are metabolized through different pathways.[11] That this is true has been amply demonstrated in the experimental animals.[69, 70] More than an isomer's being nonequivalent and therefore a nonsubstitute, it may actually have a deleterious effect, e.g., certain isomers of thiamine act as antithiamine. In a similar manner, the isomers of the essential fatty acids may act as metabolic antagonists to the natural form.[67]

Hydrogenation, as a practical commercial process, began about 1915 and its use increased steadily until at present most of the table spreads and cooking fats are highly saturated either naturally or by hydrogenation. Even peanut butter is often hydrogenated to prevent separation of oil from the peanut meat.

Other factors of significant but lesser importance in changing the quality of the fats we consume are the rising milk consumption, the increased marbling of our meats, and the increased availability of high-fat "heat and serve" prepared dishes. It is thus undeniable that coupled with a 29-per cent increase in total fat consumption, the quality of the fat also has changed.

Effect of Fat Quality on Blood Cholesterol

The importance of this change in fat quality lies in the fact that several groups of observers[4-7, 21, 23, 71-75] have conclusively demonstrated that feeding diets consisting principally of highly saturated fat results in high levels of blood cholesterol and of certain lipid

fractions of the blood. By contrast, substitution or addition to the diet of certain oils, all of which are naturally rich in linoleic or certain other polyunsaturated acids, results in a statistically significant fall of total serum cholesterol. The effects of these dietary supplements of marine and vegetable oils containing the polyunsaturated fatty acids has been maintained by the Cape Town investigators for 6 months.* This time is probably sufficient to indicate that this effect will continue in normal persons as long as adequate amounts of these oils rich in the polyunsaturated fatty acids are included in the diet.[40] This evidence seems highly significant when coupled with the observation that the middle-aged males of populations habitually consuming a high proportion of these polyunsaturated acids have much lower average blood cholesterol levels than those who consume large amounts of the highly saturated fats in countries such as the United States. This statement as yet precludes independent diseases affecting cholesterol metabolism such as myxedema, nephrosis, or idiopathic hypercholesterolemia; many diabetic subjects, however do not seem to be exceptions since they usually respond like nondiabetic individuals.

Most significantly, whenever these oils, which produce a fall in blood cholesterol, or their polyunsaturated fatty acids are hydrogenated and then fed, the favorable effect on the cholesterol level is no longer obtained.[10] This fact has been adequately confirmed.[40, 76] These fats now act to raise the cholesterol level just as do certain fats naturally highly saturated, such as butter and coconut oil.

This finding does not prove that saturation or unsaturation is the fundamental cause for changes in the cholesterol system. It may be a factor presently known, such as the amount of linoleic acid present in the metabolic mixture; it may be the proportion of the polyunsaturated acids, chiefly linoleic, to the amount of saturated fats; or it may be a factor, as yet unknown, that is intimately associated in nature with these polyunsaturated fatty acids.

Ahrens and his co-workers seem to be inclined to the total unsaturated theory, as expressed by the iodine number. Kinsell[65] and Sinclair[77] are more inclined to a concept of essential fatty acid deficiency; while Keys and his co-workers[78] lean toward a balance between the saturated: polyunsaturated fatty acids with mono-unsaturated fatty acids playing a neutral role.†

Keys et al.[79] have developed a formula for predicting the change ($\triangle$) in blood cholesterol when persons under constant metabolic conditions are subjected to changes in dietary fat. The fats tested include coconut oil, olive oil, lard, corn oil, cottonseed oil, sunflower seed oil, butterfat, safflower seed oil, and sardine oil as well as the mixed fats of the usual American diet. The amounts of the fats tested range from about 8 per cent to slightly over 40 per cent of the total calories of the diet. The Keys' formula follows:

$$\triangle \textit{ cholesterol} = 2.74 \triangle S - 1.31 \triangle P$$

where $\triangle$ cholesterol is the average change in mg. of total cholesterol per 100 ml. of serum, $\triangle$ S is change in saturated fatty acid intake as per cent of total calories, $\triangle$ P is change in polyethenoid fatty acid intake as per cent of total calories.

In practical terms this formula indicates that the cholesterol-raising effect of 1 Gm. of a saturated fat can be offset by 2 to 3 Gm. of a high-linoleic acid oil such as corn, cottonseed, or sunflower seed. Thus the removal of 1 Gm. of butterfat from the diet has about the same serum cholesterol-lowering effect as

*Since this paper was submitted for publication, this observation has been further confirmed in 79 free-living normal weight men aged 50 to 59. (As reported by Jolliffe, N., Rinzler, S., and Archer, M., at the Annual Meeting of the National Vitamin Foundation, March 3, 1959.)

†Since this paper was submitted for publication, Ahrens et al. have published an interesting observation made on 2 subjects that menhaden oil, low in linoleic acid but high in certain other polyunsaturated fatty acids, lowers the blood cholesterol as effectively as corn oil. (Ahrens, E. H., et al.: The effect on human serum-lipids of a dietary fat, highly unsaturated but poor in essential fatty acids. Lancet 1: 115, 1959.)

the addition of 2 to 3 Gm. of one of the high linoleic acid oils. In practical dietetics it would seem that the simple addition of an oil high in linoleic acid to the presently high-fat diet (40-45 per cent) would require impractically large additions (3 oz. = 810 calories or more). The subject would be confronted with a choice of either cutting down iso-calorically on the protein and carbohydrate portions of the diet and risk deficiencies in proteins, minerals, and vitamins or of becoming obese. On the other hand, restricting the saturated fatty acids to about 10 per cent of the calories in the diet with 10 per cent or more from polyunsaturated fatty acids derived from vegetable seed oils, fish and other marine sources, and from grains, vegetables, and fruits permits a palatable gourmet-type diet, one that lowers the blood cholesterol in the majority of persons and which contains as much or more protein, minerals and vitamins than the present diet high in saturated fat and "empty calories" and low in polyunsaturated acids.

The previously noted discrepancies between the total fat-coronary heart disease association, particularly in certain high-fat, low-death rate countries such as Norway, Sweden, and Denmark, may now be explained by the high proportion of fat derived by the people of these countries from fish, marine, and vegetable oils containing relatively large amounts of the polyunsaturated fatty acids, a possibility suggested by J. M. Morris (1956)[59] and recently elaborated by Jolliffe and Archer.[60] In Norway, Sweden, and Denmark, these oils make a major contribution to the total fat consumption instead of their minor role in the American diet. Panel I of figure 1 shows the coronary heart disease-total fat association while Panel II shows the correlation when unhydrogenated fats derived from vegetables, fruit, nuts, grains, and marine sources are subtracted from the total fat.[60] The latter association is very high and explains almost 70 per cent of the deviation from the straight line relationship. The countries appearing in the lower right hand quadrant of Panel I are no longer exceptions

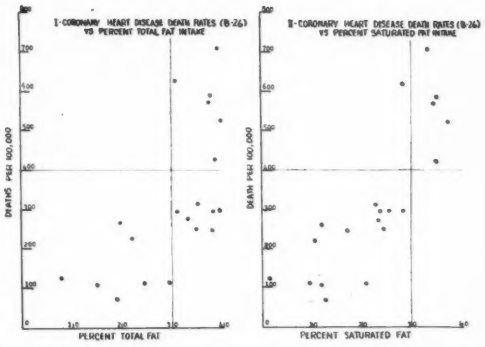

FIG. 1. Association of international death rates of coronary heart disease with percentage intakes of total and saturated-types of fat.

that tend to discount the fat-coronary heart disease postulate.

Blood Cholesterol and Coronary Heart Disease

It has been demonstrated without contradiction that populations with a high average total blood cholesterol in their middle-aged men (over 220 mg. per 100 ml.) have a high rate of coronary heart disease. Keys[21] pointed out that 2 rules hold: First, "Whenever a population has a relatively high serum cholesterol average for its clinically healthy males—220 mg. per 100 ml. or more for middle-aged men—that population exhibits a relatively high incidence of coronary heart disease. Examples are men in many parts of the United States, in London, Malmo, Sweden, Netherlands, Western Germany, upper-class men in Madrid, and Europeans in Cape Town, South Africa." Second, "Populations with low serum cholesterol averages—less than 200 mg. per 100 ml. for middle-aged men—exhibit relatively little coronary heart disease. Examples are men in Southern Italy and Sardinia, poor men in Madrid, Bantu in Johannesburg and Cape Town, Guatemalan Indians, Natives in Nigeria, and Yemenite Jews. Cape Coloured men in South Africa and men in Bologna may be intermediate examples." Major exceptions to these generalizations have not yet been found in population studies.

TABLE 6.—*Distribution of Definite New Events by Tertile (Calculated from Cooperative Study*[80])

Tertile	Per cent of new events
1	17.5
2	29.8
3	52.7

In our country the report of the cooperative study of lipoproteins and atherosclerosis[80] throws much light upon this subject, particularly from an epidemiologic point of view. In this study, a single blood cholesterol determination was made on 4,914 men who were then followed for "new events" over the next 1 to 2 years. The average blood cholesterol of this group of men, aged 40 to 59, was 240 mg. per 100 ml. As a group, over this short period of time, 2.58 times as many men who had blood cholesterols above 240 developed a definite "new event" as did those whose blood cholesterols were below 240. This study does not indicate that a single blood cholesterol determination has any considerable value in predicting a "new event" for an individual in a year or two. It is, however, of significant epidemiologic value. If an analysis of definite "new events" is made by tertile as in table 6. it becomes clear that the third of the American male population of this age group with the highest blood cholesterol has 3 times the probability of suffering such an event as those in the lowest tertile, where prudent men would prefer to be.

Population studies thus indicate a very definite relationship between (1) the amount and quality of the fat consumed, (2) the beta-lipoprotein fraction, and (3) the death rate from coronary heart disease in middle age.

With respect to the quality of the fatty acid involved, Rutstein et al.[81] have shown in vitro, how a polyunsaturated fatty acid (linolenic) prevented the intracellular deposition of lipoid that had been caused by the addition of cholesterol to tissue cultures of human aortic cells. Rutstein et al. concluded that in these cultures in a medium containing human blood serum, deposition of lipoid can be (a) induced by adding cholesterol, (b) reversed by replacing the cholesterol-containing medium by normal medium, (c) prevented by adding linolenic acid (a polyunsaturated fatty acid), and (d) potentiated by adding stearic acid (a saturated fatty acid).

The triangular relationship just noted between fat quantity and quality, coronary heart disease, and cholesterol level does not prove that a high blood level of cholesterol is the cause of atherosclerosis or of intra-arterial thrombosis. It does, however, demonstrate an uncomfortably close association which is further supported by the higher prevalence of coronary heart disease in indivduals with diabetes, myxedema, nephrosis, and lipo-dystrophies in which hypercholesterolemia is a common factor. It is still further supported by the fact that the occurrence of myocardial infarction in patients with active hyperthyroidism is almost unknown, an association not generally appreciated and called to our attention by Littman, Jeffers, and Rose.[82] It also correlates well with the fact that male castrates not only have a low blood cholesterol but seldom have coronary thrombosis and, with the corollary observation that in female castrates, high blood cholesterol levels are found along with frequent coronary heart disease.

Speculation on the Role of Fat Quality in the Pathogenesis of Coronary Heart Disease

Upon recognizing that there are degrees of susceptibility mediated by such unalterable factors as sex, race, heredity, and body constitution, and that such other environmental factors as physical activity, obesity, and excess tobacco play a role, it is apparent that the amount and type of fat intake are a major etiologic factor. Major differences of the order of 4:1 or more in death rates between countries reasonably can be explained only this way. One may even go so far as to state that without a high intake of saturated and hydrogenated fats, other factors such as stress and strain, physical indolence, obesity, luxury

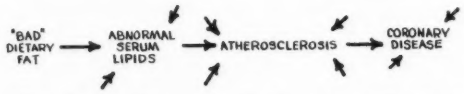

FIG. 2. Possible pathway from ingested fat to coronary heart disease (after Ahrens et al.[76]). *(Reproduced with the permission of the Journal of the American Medical Association.)*

living, or tobacco probably play only a minor role in producing a high rate of coronary heart disease in persons under 65 years of age. One may even reverse this statement and state that with an adequate intake of the polyunsaturated fatty acids these factors play but a minor role. It is also equally evident that there are nonsusceptible persons who can tolerate, over a long lifetime, large amounts of naturally saturated fats. Unfortunately, there is no method presently available by which such persons can be recognized with certainty in advance. One may briefly speculate, as did Sinclair[77] that the greater the saturated fat intake, the greater is the requirement for polyunsaturated fatty acids.

One can also follow with considerable confidence the cautious provisional judgment of Kinsell et al.[65] that linoleic acid is a dietary "essential" for adults and that an early manifestation of its deficiency is an elevated plasma cholesterol. It is not clear whether atherosclerosis results from elevated cholesterol levels per se or as separate manifestations of certain polyunsaturated fatty acid deficiency. Still unknown is the relative importance of the role played by fats in intravascular clotting directly vs. atherogenesis. Information is now sufficient to develop provisional schema of possible roles of fat in the development of coronary heart disease. The schema given in figure 2 was that developed by Ahrens et al.[76] As pointed out by Ahrens, the relationship between abnormal serum lipids and atherosclerosis may not be one of cause and effect. "Hypercholesterolemia and arteriosclerosis may both be genetically determined and the two manifestations of the disease need not be causally related." Wilkinson[63] studied many members of a familial group with hypercholesterolemia and found no greater incidence of coronary disease in the members who had hypercholesterolemia than in those whose serum cholesterol was "normal."

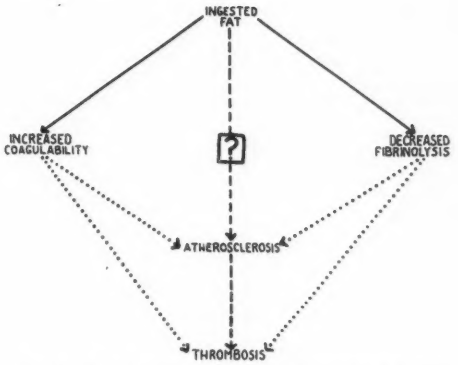

FIG. 3. Possible pathways from ingested fat to coronary heart disease (After O'Brien.[84]). ————> Highly probable to proved; - - - - -> possible to probable; . . . . . .> theoretical. *(Reproduced with the permission of the American Journal of Medical Science.)*

The next schema was that of O'Brien[84] (fig. 3) who brought into the picture blood clotting and fibrinolysis, but left with a large question mark the effects of dietary fats on the blood lipid levels. It seems that there is now sufficient evidence to extend O'Brien's schema further and derive one that can serve as a basis for further discussion (fig. 4). This schema includes the 3 possible pathways that "bad" dietary fats (which is equivalent to absolute or relative polyunsaturated fatty acid deficiency) may lead to coronary heart disease. The direct line through the center is essentially the Ahrens' schema. The line between "bad" dietary fat and abnormal blood lipids is solid to indicate its firmness. The accentuating and retarding factors recognize the modifications introduced by gonadotropic and thyroid hormones, conditional factors, and such disease factors as diabetes, nephrosis, and idiopathic lipodystrophies. The line between abnormal blood lipids and atherosclerosis is broken as this is not yet proved to the complete satisfaction of many people. The double-shafted arrow at "abnormal blood

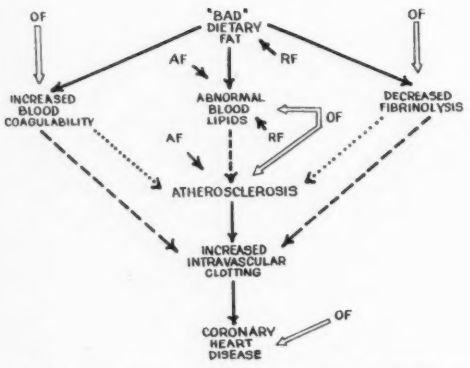

FIG. 4. Revision of possible pathways from ingested fat to coronary heart disease. ————> Highly probable to proved; - - - - -> possible to probable; . . . . .> theoretical; AF————> accentuating factors, e.g., genetics, hormones, diabetes, nephrosis, maleness; RF————> retarding factors, e.g., genetics, hormones, femaleness; OF=====> other factors outside schema unrelated to dietary fats.

lipids'' and ''atherosclerosis'' is to include Ahrens' caution among others that hypercholesterolemia and atherosclerosis may both be genetically determined and that the 2 manifestations need not be causally related. The line between atherosclerosis and increased intravascular clotting, modified, of course, by chance location of the atheromatous plaques, is solid, for slowing of the blood stream by severe narrowing of the arterial lumens is recognized, with all other factors equal, as promoting intravascular clotting. But ''bad'' dietary fats do not necessarily have to produce coronary heart disease through the atherogenic pathway. The increased blood coagulability and decreased fibrinolytic activity of certain dietary fats seems established; just how important these 2 factors are in vivo has not been conclusively demonstrated but it seems more probable than just possible that they are important. These 2 influences, if effective in vivo, could only lead to increased intravascular clotting, especially when associated by a slowing of the blood stream by an atherosclerotic plaque. The double arrows pointing to these 2 pathways recognize non-''bad'' dietary factors. It may well be that these 2 factors, increased coagulability and decreased fibrinolysis, account for the presence or absence of clinical coronary heart disease in persons with relatively equal amounts of coronary atherosclerosis. The double arrow pointing to ''coronary heart disease'' recognizes the other etiologic factors producing coronary heart disease such as aneurysms, embolizations, etc.

This schema is attractive for it affords a reasonable explanation of certain apparent contradictions in our knowledge of coronary heart disease, such as the relative immunity of women prior to the menopause. At this time their requirements for fatty acids are presumably much lower than those of men.[77] The low incidence of coronary artery disease among certain high-fat-consuming groups may be attributed to their high intakes of polyunsaturated fatty acid. This theory also explains why the most affluent and the most advanced countries industrially, where the economy permits most people sufficient income for a luxury diet high in saturated fat, are the ones in which coronary heart disease has increased and is still increasing the most. It is also in these countries with high fat consumption that the most fat is hydrogenated, and the formation of isomers of the essential fatty acids may act physiologically as anti-essential fatty acid, like the isomers of thiamine, which act as antithiamine. It helps explain why coronary heart disease during World War II decreased in Norway when the occupying Germans commandeered the butterfat while their hydrogenation plants were destroyed by air action.

The next steps in tranferring these results from metabolism ward and formula diets to public health practice are as follows[3]:

1. Develop practical diets to replace metabolism ward and formula diets for the general public. These diets must be of nutritionally balanced, palatable and acceptable American foods which are available in every grocery store.

2. Demonstrate by public health methods that, if persons in their usual environment

can be induced to modify their diets over a long period of time, their blood lipids, as measured by the cholesterol-lipoprotein system, will be favorably influenced.

It remains to be proved, however, that a significant number of persons free-living and consuming common American foods can be so induced. This is in reality a clear challenge to our ability to motivate and educate so that a change in the diet of free-living persons will result.

3. Demonstrate whether a favorable change in the cholesterol-lipoprotein system produced and maintained by diet is associated in fact with a favorable change in morbidity and mortality from coronary heart disease, particularly in men under 65 years of age. From the evidence presently known it seems not too optimistic to predict that an answer to this can be given within a few years.

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CLINICAL CONFERENCE

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Rupture of the Ventricular Myocardium and Perforation of the Interventricular Septum Complicating Acute Myocardial Infarction

By WILLIAM L. PROUDFIT, M.D., FERNANDO A. TAPIA, M.D., LAWRENCE J. MCCORMACK, M.D., AND DONALD B. EFFLER, M.D.

ONE of the fatal complications of acute myocardial infarction is rupture of the affected ventricular myocardium. The free wall of the left ventricle is the region usually involved, and sudden death occurs due to acute cardiac tamponade. Occasionally the interventricular septum is perforated, and the clinical signs are characteristic. Recognition of septal perforation may permit utilization of surgical correction of the defect in suitable cases. The following case is presented and discussed to emphasize the clinical signs of rupture of the myocardium and interventricular septum.

CASE HISTORY

A 56-year-old dock worker was admitted to the hospital on April 28, 1957, because of pain in the anterior portion of the neck and left shoulder. He had been well previously. On the day of admission he went to sleep at 2 p.m. but was awakened 2 hours later by severe pain in the neck and left shoulder and mild upper substernal discomfort. On admission, the temperature was 97 F., the pulse rate was 48 per minute, and the blood pressure was 104/70 mm. Hg. No significant abnormalities were found on complete physical examination. The urinalysis, blood counts, erythrocyte sedimentation rate, blood sugar value, cholesterol content of the plasma, and serologic reactions were normal. Subsequently, the serum glutamic oxalacetic transaminase content rose as high as 140 units per ml. An electrocardiogram made on admission showed sinus bradycardia and changes in the Q wave and S-T segment consistent with acute posterior myocardial infarction.

At 11:30 p.m. on the day of admission the patient noticed a mild aching in the left shoulder. His pulse rate was 60 per minute and his blood pressure was 90/70 mm. Hg. The following afternoon he developed pain in the neck and his blood pressure fell to 80/60. Sympathomimetic drugs administered intramuscularly and intravenously were required to maintain the arterial blood pressure. At 11:45 p.m., 2 days after admission, he had severe pain in the neck and upper substernal area. For the first time a loud systolic murmur was heard along the left border of the sternum over the fourth intercostal space and the murmur was accompanied by a thrill; the pulse rate was 120 per minute. The following morning he had mild pain in the neck and substernal area. The murmur was unchanged, the neck veins were distended, and the lungs were clear. At noon he suddenly developed gasping respirations, followed by a generalized tonic convulsion and death.

DISCUSSION

DR. WILLIAM L. PROUDFIT: It is apparent that this man had an acute myocardial infarction. The localization of the pain was unusual in that the severe pain was in the anterior neck and left shoulder and only minor discomfort was experienced in the upper substernal area. The other feature of interest in the early portion of his illness was

From the Departments of Cardiovascular Disease, Anatomic Pathology, and Thoracic Surgery, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

the bradycardia. Tachycardia is regarded as an unfavorable prognostic sign in acute myocardial infarction, especially if it persists after the first 24 hours. On the other hand, sinus bradycardia is not necessarily a favorable sign; it may be encountered early in the course of extensive myocardial infarction.

Except for difficulty in maintaining the arterial blood pressure, the patient progressed fairly well until the evening of the second day, when he had severe pain and a loud precordial systolic murmur was heard for the first time. Few conditions could account for the sudden development of a murmur and thrill in such a case. Rupture of a papillary muscle, secondary to myocardial infarction, would result in a loud murmur. However, the murmur is usually loudest at the cardiac apex rather than along the left border of the sternum. Furthermore, pulmonary symptoms and signs appear rapidly in this condition, but this patient's lungs were said to be clear and no mention of dyspnea was made. Perforation of the interventricular septum is another serious complication of acute myocardial infarction. The murmur and thrill usually are maximal along the left border of the sternum in the fourth intercostal space and rapid rise in the venous pressure occurs, as was described in this case. The murmur resembles that of congenital interventricular septal defect. A rupture of the aortic valve would result in a diastolic murmur and it would not be expected to occur in the course of acute myocardial infarction. A systolic or diastolic murmur might occur suddenly in dissecting aneurysm, but the described localization of the systolic murmur would not be expected in dissecting aneurysm, and the course of the disease does not seem to be consistent with that condition.

Doctor Tapia, you have been interested in auscultation of the heart. Did you listen to this man's heart or record his sounds?

Dr. Fernando A. Tapia: There were no heart murmurs at the time of admission or during the first 48 hours of hospitalization. He then developed a grade-IV, rough holosystolic murmur, which could be heard over the entire precordium but which was distinctly loudest over the fourth intercostal space at the left sternal border; it was associated with a palpable thrill at this level. These findings were detected when the patient was examined because of severe pain in the upper substernal area and neck. A phonocardiogram recorded on magnetic tape the following morning confirmed the auscultatory findings; the murmur had large vibrations of high frequency and there was some midsystolic increase in intensity.

While the phonocardiogram was being made, the patient suddenly developed gasping respirations and transient generalized tonic convulsions. The simultaneous and continuous electrocardiographic and phonocardiographic recording (fig. 1) showed rapid decrease in the intensity of the heart sounds and systolic murmur until they disappeared completely with cessation of the vital signs. However, the electrocardiogram remained unchanged and a normal sinus rhythm continued for several minutes after the patient's clinical death. In the attempt to restore his vital functions by artificial respiration and rapid intravenous infusion of drugs, the microphone was removed temporarily from the chest wall. Two minutes later the microphone was replaced; unchanged electrocardiographic complexes were recorded for 2 or 3 more minutes, but cardiac sounds could not be heard nor could they be recorded graphically. The QRS complexes then gradually became bizarre and broad, and the ventricular rate became slower and irregular until there was complete cessation of ventricular activity.

Dr. Proudfit: From Dr. Tapia's discussion, it seems necessary to conclude that this man had a perforation of the interventricular septum secondary to acute myocardial infarction. The findings at the time of death are important. It is apparent that the patient did not have a "mechanism death." I believe that actual "mechanism deaths" in the course of acute myocardial infarction are infrequent. It is true that ventricular fibrillation is a terminal event frequently, but usually it is

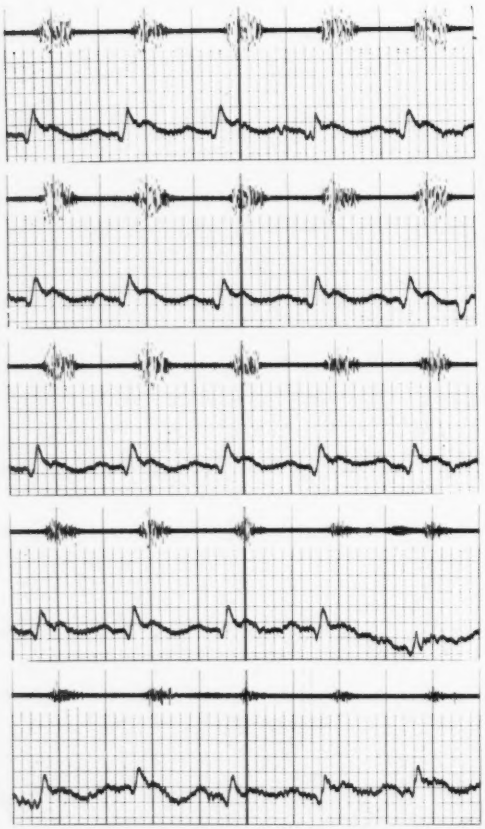

FIG. 1. Electrocardiogram and phonocardiogram taken immediately before death (paper speed 75 mm. per second in transcription from magnetic tape recording).

obvious that death is imminent prior to the development of the arrhythmia. In many other cases the heart simply stops. In this instance neither situation was encountered. The electrocardiogram remained unchanged after clinical death. The fact that the cardiac sounds rapidly became distant just prior to death suggests that something was interfering with the transmission of the sounds or was severely and progressively limiting the diastolic filling or systolic contraction of the heart. The occurrence of a convulsion is consistent with a severe reduction in cardiac output. Rupture of the free wall of the left ventricle with resultant acute cardiac tamponade could be responsible for the findings described.

DR. LAWRENCE J. MCCORMACK: Although this necropsy was limited to the heart, it demonstrates once again how much information can be obtained when even a limited examination is granted. The pericardial sac contained about 300 ml. of partially clotted blood. The heart weighed 410 Gm., the region of greatest enlargement appearing to be the left ventricle. A red, soft, granular area 5 by 5 cm., straddling the septal region, was seen on the posterior surface of the heart. At the inferior margin of this area was a 1-cm. rent (fig. 2). Usually the site of rupture is anterior or lateral. There was variation from the usual pattern of coronary circulation: the posterior circulation of this heart was derived from the left circumflex coronary artery. This artery (the "Achilles' heel" of this heart) had become atheromatous and a superimposed recent thrombus was located 5 cm. from the origin of the artery. The remaining dissectable coronary vessels showed minimal atherosclerosis. When the left ventricle was opened, a laceration, 2.5 cm. in diameter, was found posteriorly 4 cm. from the apex at the junction of the septum and the posterior myocardium (fig. 3). A probe was passed with ease through it and through the externally visible point of rupture. The origin of the internal rent and this dissection channel formed one limb of a Y. Another limb was formed by a channel that passed into the right ventricle with a slit-like orifice located near the base of the medial papillary muscle; this rent was 1.0 cm. in length. The area of destruction of myocardium, represented by softened muscle, seen on a cross section occupied the posterior half of the septum and most of the posterior surface of the left ventricle, and appeared to involve the entire thickness of the myocardium. Microscopic examination of the damaged area disclosed muscle fibers with loss of cross striations, eosinophilia, and swelling with considerable intermingled hemorrhage. There was also a profuse infiltrate of polymorphonuclear leukocytes, far in excess of that usually seen in myocardial infarction but of the degree commonly encountered when rupture of the heart has occurred. No other

anatomic abnormalities were found within the heart. The anatomic diagnoses are (1) atherosclerosis of the left circumflex coronary artery with superimposed recent thrombus formation; (2) anatomic variation of arterial pattern with the left circumflex coronary artery supplying the posterior surface of the heart; (3) myocardial infarction, recent, transmural, posterior; (4) posterior rupture of the myocardial infarct into the pericardial sac with hemopericardium (300 ml.); (5) rupture of the interventricular septum, small, recent; and (6) cardiomegaly (410 Gm.).

Doctor Effler, you have had experience with the surgical treatment of perforation of the interventricular septum. Would you discuss this complication? Do you think you could have offered effective surgical repair in this case?

Dr. Donald B. Effler: It would be correct to say that I have had *an* experience with surgical closure of an interventricular septum following myocardial infarction. The patient, a 54-year-old man, was referred to me approximately 6 months after the infarction had occurred. His initial recovery from the acute myocardial infarction apparently had been fairly satisfactory until the perforation occurred. A systolic murmur which could be heard over the precordium suddenly developed, and at that time, he developed congestive heart failure with a significant increase in the size of the heart. The diagnosis of interventricular septal defect was suspected and was confirmed by cardiac catheterization.

The operation for closure of the interventricular septal defect was undertaken almost 2 years ago. A pump oxygenator was employed for total bypass; in addition, we utilized elective cardiac arrest (Melrose technic). Although there was considerable concern over the patient's coronary artery disease, it did not prove to be a factor in his recovery, and his progress has been gratifying. Subsequent studies done by means of cardiac catheterization almost a year after the operation showed the persistence of the shunt but considerable reduction in its magnitude as compared to that found at the initial study.

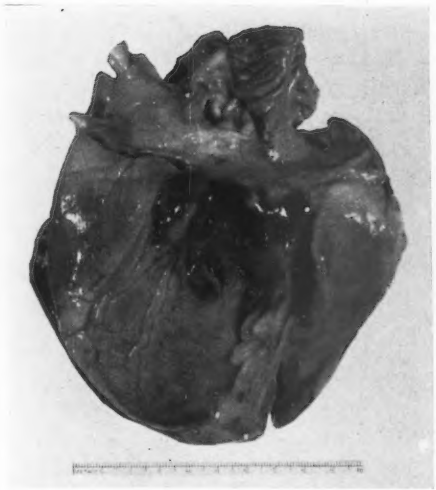

Fig. 2. Gross photograph of posterior surface of heart showing area of discoloration and external site of perforation of myocardium.

Fig. 3. Internal view of left ventricle with anterior leaf of mitral valve transected to show extent of internal laceration.

The septal defect was located low on the posterior aspect of the septum. It was roughly the size of a nickel; the edges were smooth and the defect was roughly circular. Surgical closure was effected by direct suturing. No prosthetic patch was employed. Perfusion of the coronary circulation must have been adequate, because the arrested heart started

promptly without arrhythmia, and there were no problems related to coronary insufficiency during the postoperative period. Although the defect was created by local ischemia, healing did take place to such an extent that most of the shunt has been abolished.

My conclusion, based on this 1 successful case and the review of 2 autopsy specimens is that successful closure of an acquired ventricular septal defect of the post-infarction variety will probably be limited to those who survive the initial insult and the acquired shunt for a significant period of time. It is quite unlikely that the patient with acute perforation and its attendant complications will tolerate successful surgical closure.

Roodenburg, A. I.: Secondary Hypertrophic Osteoarthropathy. New York State J. Med. 58:3635 (Nov. 15), 1958.

Secondary hypertrophic osteoarthropathy refers to the syndrome of clubbing of the digits, periosteal proliferation with pericortical deposition of bone, and arthritis incidental to a major visceral disease. It occurred most commonly in relationship to pulmonary, pleural, or mediastinal disease. It did not seem to occur most frequently incidental to pulmonary malignancy, but in that association it appeared to develop more rapidly and was more painful. Various theories in etiology have been suggested. It was claimed that pulmonary malignancy produced a factor responsible for clubbing. Cyanosis has long been considered in the pathogenesis of secondary hypertrophic osteoarthropathy. In the clubbing associated with cirrhosis it has been suggested that the phenomenon was due to circulating estrogens or related substances. Sectioning the vagus nerve in the chest was followed by regression of the secondary disease even when the pulmonary tumor could not be removed. Since each of these factors cannot be implicated in every patient with secondary pulmonary osteoarthropathy, the pathogenesis must still be considered unknown. The directly inciting factor may be tissue hypoxia, which may be the result of a number of different mechanisms.

KRAUSE

ABSTRACTS

HYPERTENSION

Hajdu, S., and Leonard, E.: A Serum Protein System Affecting Contractility of the Frog Heart Present in Increased Amounts in Patients with Essential Hypertension. Circulation Research **6**: 740 (Nov.), 1958.

Serum from patients with severe essential hypertension has been previously shown to have a cardiotonic action on the isolated frog heart. A system of 3 proteins in plasma responsible for this activity has been characterized within the globulin group. One component, termed L protein, became strongly bound to the bioassay frog heart but the other 2 components comprised a washable fraction. Calcium was bound to the O-17 washable fraction and the calcium could be released by the addition of the L component to the system. The protein system described caused contracture of frog heart muscle in the absence of ionic calcium, in contrast to other contracture-causing agents such as strophanthidin and digitonin, which required free calcium for activity. The authors suggested that the biological activity of the protein system on the frog heart may be achieved by delivering calcium from component O-17 to the contractile mechanism.

PAUL

METABOLIC EFFECT ON CIRCULATION

Book, M. H., Greene, E. A., and Lorber, V.: Effect of Purine and Pyrimidine Ribosides on an Isolated Frog Ventricle Preparation. Circulation Research **6**: 735 (Nov.), 1958.

Various purine and pyrimidine ribosides (cytidine, uridine, thymidine, guanosine, and inosine) with the exception of adenosine were reported to exhibit a positive inotropic effect on an isolated strip of frog ventricle. In a preparation already responding maximally to 1 test compound, the addition of a second compound led to a further increase in tension. The authors suggested from the findings that the various ribosides acted, at least in part, through independent mechanisms. These compounds probably participated as co-factor precursors in a variety of enzymatic reactions. The gradual mechanical failure of the isolated ventricle strip preparation may result from depletion of the various quantitatively lesser nucleotide co-factors. The failure of adenosine to exhibit a positive inotropic effect may result from the abundance of adenosine nucleotide in the cell.

PAUL

Gemmil, C. L.: Cardiac Hypertrophy in Rats and Mice given 3, 3′, 5-Triiodo-L-Thyronine Orally. Am. J. Physiol. **195**: 385 (Nov.), 1958.

The effects of 3, 3′, 5-triiodo-L-thyronine (T-3) upon the metabolism and circulation were measured in rats and mice. During the oral administration of T-3 there was a marked and sustained rise in metabolism, which disappeared when the T-3 was discontinued. The heart rates of both the rats and mice given T-3 were greater than those of the control animals. This increment in weight was not due to an increase in water content of the hearts. In the rat, following the removal of the T-3 in the drinking water, there was a return of the heart to approximately normal size. There were no abnormal electrocardiographic findings during the hypermetabolic state.

KAYDEN

Wallach, E. E., Lubash, G. D., Cohen, B. D., and Rubin, A. L.: Cardiac Disease and Hypothyroidism. J.A.M.A. **167:** 1921, Aug. 16, 1958.

Specific replacement therapy in hypothyroidism often gives rise to cardiac complications. Such complications are more related to initial vigorous treatment than to total thyroid dosage. Arteriosclerotic heart disease increases the risk, and the presence of this disease may be implied by evidence of arteriosclerosis in other sites. Thyroid therapy reverses anatomic changes that have occurred in the heart in hypothyroidism and may call upon an enlarged heart for function above its physiologic capacity. Therapy in patients with possible heart disease and hypothyroidism should be instituted with low doses and gradual increments.

KITCHELL

PATHOLOGY

Heath, D., and Edwards, J. E.: Configuration of Elastic Tissue of Aortic Media in Aortic Coarctation. Am. Heart J. **57:** 29 (Jan.), 1959.

Histologic examination of sections of the aorta proximal and distal to the site of coarctation was performed in 9 patients. No structural changes in the elastic tissue ascribable to inactivity could be found. On this basis it was concluded that, although the blood pressure in the aorta distal to the coarctation was relatively decreased, the absolute level of mean pressure present in this segment of the aorta must have been high enough to maintain the normal configuration of aortic elastic tissue.

SAGALL

Bryant, R. E., Thomas, W. A., and O'Neil, R. M.: An Electron Microscopic Study of Myocardial Ischemia in the Rat. Circulation Research **6:** 699 (Nov.), 1958.

The authors described the early ultrastructural changes observed in the ischemic rat myocardium following ligation of the anterior descending branch of the left coronary artery. Although light microscopy could not detect histologic abnormalities in infarcts of 5 hours or less duration, electron microscopy showed striking changes after 1 hour. These early changes consisted mainly of swelling of the mitochondria and the sarcoplasmic reticulum followed by an increase in lipid droplets. The abnormalities in the ultrastructure of the myofiber were believed to reflect the hyperosmolarity that resulted from anoxia.

PAUL

PHARMACOLOGY

Jourdan, F., Duchene-Marullaz, P., Faucon, G., and Bouverot, P.: An Experimental Study of the Action of Methoxypromazine on the Cardiovascular and on the Autonomic Nervous Systems. Arch. int. Pharmacodyn. **117:** 341 (Nov.-Dec.), 1958.

The effects of a previously described derivative of chlorpromazine, methoxypromazine (Mopazine) on the cardiovascular and autonomic nervous systems was investigated in the dog. The usual dose was 3 mg./Kg. Unlike chlorpromazine, methoxypromazine did not accelerate the heart rate; transient acceleration was noted only as a brief compensatory reaction to the hypotension produced in the unanesthetized animal. With chloralose anesthesia, on the other hand, a profound hypotension was observed, the result of the peripheral vasodilator effect of the drug. This effect was confirmed following destruction of the spinal cord and also by peripheral flow measurements following intrarterial injection. Like chlorpromazine, methoxypromazine suppresses hypertension induced by epinephrine. The reasons for the different action in the anesthetized animal are discussed.

BRACHFELD

Pathak, C. L.: Direct Action of Acetazolamide (Diamox) on Heart. Arch. int. Pharmacodyn. **117:** 168 (Oct.), 1958.

In the isolated frog heart, acetazolamide was found to have diphasic, inotropic, and chronotropic effects. On mammalian atria the drug mainly produced a negative chronotropic effect. It was concluded that the drug is basically a cardiac depressant.

BRACHFELD

Dornhorst, A. C., and Herxheimer, A: Effects of Isoprenaline Isomers in Man. Lancet **2:** 723 (Oct.), 1958.

The properties of the l- and d-isomers of isoprenaline were compared in 3 normal volunteers by measuring the response of the heart rate and the pulse pressure to an intravenous infusion. The l-isomer was almost 50 times as potent. The subjective effects corresponded with the objective measurements and the local effects were qualitatively similar. Nevertheless, a suitable subcutaneous dose of the d-isomer had a clear-cut bronchodilator effect in a patient in status asthmaticus.

KURLAND

Kaab, W., DePaula e Silva, P., and Starcheska, Y. K.: Adrenergic and Cholinergic Influences on the Dynamic Cycle of the Normal Human Heart. Cardiologia **33**: 350, 1958.

The duration of isometric and ejection periods was measured in healthy young males by means of combined tracings of the electrocardiogram, carotid pulse and phonocardiogram. Following the recording of normal values, the effect of carotid sinus pressure, epinephrine and norepinephrine, atropine and the upright position was recorded. It was concluded that in the normal heart the duration of isometric contraction of the left ventricle is shortened by adrenergic and lengthened by cholinergic inotropic action. It remains nearly unaffected by changes of pulse rate or peripheral resistance. The elimination of the cholinergic factor by atropinization permitted indirect estimation of this factor. An adrenergic pattern was noted under emotional tension and during epinephrine infusion; the cholinergic pattern appeared during carotid sinus compression. Infusions of norepinephrine produced predominantly cholinergic effects due to secondary reflex stimulation. Atropinization uncovered the primary, specifically adrenergic action of norepinephrine.

BRACHFELD

Bass, P., Mazurkiewicz, I., and Melville, K. I.: Effects of Magnesium on Coronary Flow and Heart Action and Its Influence on the Responses to Adrenaline and Noradrenaline. Arch. Int. Pharmacodyn. **117**: 9 (Oct.), 1958.

Coronary flow and changes in heart contractions were recorded simultaneously in the isolated rabbit heart, using a modified Langendorff technic previously described. Injections of 0.025 to 2.5 mg. of magnesium chloride into the perfusing fluid, close to the heart, produced "primary" coronary vasodilatation without any apparent change in heart contractions. Larger doses (25-250 mg.) temporarily depressed the amplitude of the contractions so that the concomitant intense coronary dilatation might have been partly secondary to the associated decreased extravascular depression. Continuous perfusions with increasing concentrations (0.009-0.364 mg. $Mg.^{++}$/ml. in Locke's solution) were associated with increasing degrees of coronary dilatation without significant change in heart action (amplitude or rate). At lower perfusion concentrations of magnesium, a small dose of epinephrine (10 μ.) induced greater vasodilatation than during control, and a larger dose (100 μ.) induced the expected greater effect whereas such a dose-response relationship was lacking with norepinephrine. It was concluded that magnesium can alter coronary flow independently of heart rate and contraction and that the ion elicits different responses to epinephrine and norepinephrine by the isolated heart.

BRACHFELD

Cafruny, E. J., Domino, E. F. and Beck, L.: Adrenergic Blocking Action of Tetrazotized Diorthoanisidine. J. Pharmacol. & Exper. Therap. **124**: 219 (Nov.), 1958.

This report deals with the characterization of the adrenergic blocking action of tetrazotized diorthoanisidine (TDA). This compound combined with epinephrine, norepinephrine, and isoproterenol in vitro to produce substances that had little or no effect on blood pressure. Intravenous administration of TDA produced typical adrenergic blockade that was also apparent in isolated dog carotid and rabbit aortic strips. The positive chronotropic action of sympathomimetics was not blocked by TDA. The pressor responses to carotid occlusion and asphyxia were not blocked.

RINZLER

Aviado, D. M., Jr., Wnuck, A. L., and De Beer, E. J.: The Effects of Sympathomimetic Drugs on Renal Vessels. J. Pharmacol. & Exper. Therap. **124**: 238 (Nov.), 1958.

This report compares the renal vascular effects of all commercially available sympathomimetic drugs. This was done in anesthetized dogs by inserting a rotameter in the renal artery. Four types of responses were found. The following drugs constricted the renal vessels when injected into the renal artery and intravenously: levarterenol, epinephrine, phenylephrine, metaraminol, methoxamine, and naphazoline. The following drugs constricted the renal vessels when injected into the renal artery but produced variable effects when injected intravenously: epinephrine, phenylpropanolamine, hydroxyamphetamine, and compound 45-50 [eta-hydroxyl-beta- (2, 5-diethoxyphenyl) isopropylamine]. The following drugs had no important effect on renal vessels when injected into the renal artery; when given by vein, renal blood flow was increased as a result of their systemic pressor effect: methamphetamine, pseudoephedrine, amphetamine, pholedrine, methylaminoheptane, tuaminopheptane, mephentermine, and phenylpropylmethylamine. The following drugs had a local dilator action when given by renal artery; when given by vein, the renal blood flow was decreased as a result of their arterial depressor effect: isoproterenol, nylidrin, isoprophenamine, methoxyphenamine, and cyclopentamine.

RINZLER

Pelner, L., Waldman, S., and Rhoades, M. G.: The Problem of Levarterenol (Levophed) Extravasation. An Experimental Study. Am. J. M. Sc. **236**: 755 (Dec.), 1958.

The use of levarterenol (Levophed) is occasionally marked by the occurrence of ischemia and subsequent necrosis in an area in which the drug has infiltrated. This sequence of events can occur even in the absence of infiltration with the needle perfectly in place and the infusion running well. It has previously been established that both phenatolamine (Regitine) and piperoxan (Benodaine) can reverse the ischemia if infiltrated by multiple punctures into the ischemic area. The efficacy of several agents in the prevention of necrosis from Levophed was studied in adult rabbits in whom the intracutaneous injection of 1 ml. of Levophed (1 mg./ml.) invariably produced an ischemic area and subsequent necrosis. It was found that secondary injection with Regitine or Benodaine not later than 18 hours after the Levophed injection would prevent necrosis in each instance. Similar administration of novocaine in no instance prevented necrosis. The admixture of Meticortelone or Solu-Cortef to the Levophed enhanced the ischemia and necrosis occurred more rapidly. The admixture of heparin, however, prevented necrosis. When heparin and Meticortelone were both added to a solution of Levophed, no ischemia or necrosis ensued. The authors suggest that by the addition of 10 mg. of heparin to a solution of levarterenol being administered intravenously, ischemic necrosis might be prevented. However, they caution that in post-operative shock, even this small amount of heparin might increase the probability of bleeding and therefore should not be used.

SHEPS

Moran, N. C., and Perkins, M. E.: Adrenergic Blockade of the Mammalian Heart by a Dichloro Analogue of Isoproterenol. J. Pharmacol. & Exper. Therap. **124**: 223 (Nov.), 1958.

This report presents evidence that a dichloro analogue of isoproterenol (DCI) blocks the inhibitory, but not the excitatory, effects of sympathomimetic amines and selectively blocks the positive inotropic and chronotropic effects of adrenergic stimuli in dogs with intact circulatory systems and in isolated hearts of rabbits. In dogs complete blockade of the cardiac positive inotropic effects of small doses of epinephrine, norepinephrine, and isoproterenol and of supramaximal stimulation of the cardiac sympathetic nerves was obtained with cumulative doses of DCI of 3 mg./Kg. and greater. Depression of contractile force was frequently observed in response to sympathomimetic amines and to sympathetic nerve stimulation after administration of large doses of DCI. No inhibition of the positive inotropic effects of digoxin, theophylline, or calcium chloride was observed. In dogs blockade of the positive chronotropic effects of isoproterenol but not of theophylline was obtained with DCI. In isolated rabbit hearts DCI had qualitatively the same blocking action on the effects of the amines but not on those of calcium, theophylline, or ouabain. The dichloro analogues of epinephrine (DCE) and norepinephrine (DCNE) had similar blocking actions to those of DCI but were less potent. DCI, in both dog and rabbit heart, initially stimulated the heart but with subsequent doses depressed it. DCNE had similar effects in the dog, but in the rabbit heart it produced only depression as did DCE. The cardiac depressant effects were not antagonized by atropine. Ephedrine, which also produced initial cardiac stimulation and subsequent depression with high doses in the dog, did not inhibit the cardiac stimulation actions of other sympathomimetic amines. The vasopressor effect of epinephrine in dogs was potentiated by DCI, that of norepinephrine was relatively unchanged, while that of cardiac sympathetic nerve stimulation was blocked, presumably due to the cardiac blockade. The vasodepressor effect of isoproterenol was completely blocked, but not reversed, by DCI in the dog. DCI, on intravenous administration, transiently lowered blood pressure, while DCNE produced a prolonged rise. DCNE did not appear to inhibit the vasopressor actions of epinephrine and norepinephrine or the vasodepressor action of isoproterenol.

RINZLER

PHYSIOLOGY

Kien, G. A., Lasker, N., and Sherrod, T. R.: Action of Cigarette Smoke on Cardiovascular Hemodynamics and Oxygen Utilization in the Dog. J. Pharmacol. & Exper. Therap. **124**: 35 (Sept.), 1958.

A study was made of the effect of cigarette smoke on the time course of hemodynamic changes in the myocardium including cardiac work, coronary blood flow, and oxygen metabolism, using the anesthetized open-chest dog. There was a lack of correlation between the onset of the electrocardiographic effects and the change in cardiac work. Coronary blood flow increased and appeared to follow the changes in blood pressure and cardiac output. A marked decrease in the oxygen consumption of the heart occurred in a close time relationship to the electrocardiographic disturbances. The effects of cigarette smoke were duplicated by the intravenous injection of nicotine alkaloid.

RINZLER

Jungman, H., Erdmann, W. D., and Heye, D.: On the Nature of the Fundamental Arterial Wave (Dicrotism) and Its Significance in Hemodynamics. Arch. Kreislaufforsch. **28:** 153 (July), 1958.

The fundamental arterial wave was defined by its length, equal to the velocity of the pulse wave multiplied by the duration of the standing wave; the duration of the standing wave was given by the interval between the systolic peak and the dicrotic wave; the velocity of the pulse wave was measured by direct recording of the pulse pressure curves in the carotid and femoral arteries. The effective length of the arterial system was a constant fraction of the length of the fundamental wave. Measurements were made in 14 dogs, modifying the hemodynamic parameters of cardiac rate, blood pressure, and blood volume by vagal stimulation, by bleeding and infusion, and by intravenous or intraarterial administration of drugs. The drugs used included: agents acting directly on the arterial wall (acetylcholine, carbaminoylcholine, amylnitrite, papaverine, histamine); blockers of the nervous control (regitine, procaine, tetraethylammonium bromide, hexamethonium bromide); vasopressors (norepinephrine, vasopressin). Evidence was presented to prove that the length of the fundamental wave was in fact a physical constant of the arterial system, provided the regulation of the circulation was not impaired. Drugs increasing the blood pressure enhanced the fundamental wave. Drugs acting on the wall of the arteries, directly or through the nervous control, prolonged the duration of the wave: carbaminoylcholine, regitine, and the ganglionic blockers were the most active of the drugs tested; in higher dosage all these drugs obliterated the fundamental wave; this may result from marked decrease of the peripheral resistance and of the mean arterial pressure. The fundamental wave should not be considered an unavoidable imperfection of the arterial system; its hemodynamic significance is stressed.

CALABRESI

de Burgh, Daly, M., and Luck, C. P.: The Effects of Carotid Sinus Baroreceptor Reflexes on Pulmonary Arterial Pressure and Pulmonary Blood Flow in the Dog. J. Physiol. **143:** 343 (Sept. 23), 1958.

Reflex changes in mean pulmonary blood flow that occurred in response to alterations in carotid sinus pressure were studied in the dog. Heparinized dog's blood was perfused through innervated carotid sinuses that were isolated from the circulation. Pulmonary lobar blood flow, total pulmonary blood flow, and combined blood flow through the superior and inferior venae cavae were measured by means of a rotameter flow meter. Occlusion of the common carotid arteries produced tachycardia, a rise in systemic and pulmonary arterial blood pressure, and an increase in pulmonary blood flow; these effects were enhanced by division of the cervical vagosympathetic nerves. Stimulation of the baroreceptors by raising the perfusion pressure of the carotid sinus produced bradycardia, a fall in systemic and pulmonary arterial blood pressure, and a decrease in pulmonary blood flow and volume. The pulmonary arterial pressure and blood flow partly recovered despite continued increased carotid sinus pressure, and there was an afterrise in these values when the sinus pressure was released. The authors suggested that the reduction of the pulmonary blood flow and pulmonary arterial pressure on stimulation of the carotid sinus baroreceptors was due to reflex bradycardia and hemodynamic events occurring in the peripheral circulation. Distention of the carotid sinus also produced a decrease in total peripheral vascular reflexes, a small increase in pulmonary vascular resistance, and a decrease in the stroke work of both ventricles. The changes in the left and right atrial pressures were small and quite variable.

KARPMAN

Field, L. W., and Laverty, R.: Nervous Humoral Responses to Acute Blood Loss in the Rat. J. Physiol. **143:** 213 (Sept. 23), 1958.

A constant output arterial pump was used to perfuse blood from a donor rat through an innervated, but otherwise isolated, hind limb of a recipient rat. The use of this technic made it possible to distinguish changes in vascular tone due to nervous factors from those due to humoral factors. Blood was then withdrawn from the carotid artery of the recipient animal until its blood pressure was reduced to 30 mm. Hg. In 8 experiments it was evident that acute blood loss did not result in any nervous responses causing appreciable compensatory changes in the blood vessels of the hind limb. In fact, repeated acute blood loss resulted in increasing vasodilatation in the perfused limbs. In the second group of experiments the hind-limb vessels were cannulated, all vessels and nerves were ligated, and the animals were then killed. The first acute blood loss in the donor rat resulted in a slight rise in perfusion pressure in the hind limb and repeated episodes of acute blood loss produced pressor responses of increasing magnitude. No marked increase of reactivity in these limbs to norepinephrine or to pitressin was noted. Experiments in which the kidneys or the adrenal glands, or both, were removed suggested that a vaso-

constrictor substance which came from neither the kidney nor the adrenal gland, was released or activated during blood loss. There was some suggestion that the presence of the adrenal gland decreased the vasoconstrictor response and the presence of the kidney tended to increase it.

KARPMAN

Black, J. E., and Roddie, I. C.: The Mechanism of the Changes in Forearm Vascular Resistance During Hypoxia. J. Physiol. **143**: 226 (Sept. 23), 1958.

Respiratory movements, intraarterial blood pressure and forearm blood flow (by venous occlusion plethysmography) were measured in 4 healthy, young adults. Hypoxia produced by breathing 5-10 per cent oxygen in hydrogen produced a large increase in ventilation, heart rate, and forearm blood flow. There was relatively little change in mean arterial or venous pressure, so that the vascular resistance (calculated by dividing mean perfusion pressure by mean flow) was considerably reduced. When excess of carbon dioxide was breathed the mean arterial pressure increased, the blood flow fell slightly, and the vascular resistance was increased. The vascular resistance in the nerve-blocked forearm was reduced by hypoxia and it was therefore postulated that forearm vasodilatation with hypoxia was due to humoral rather than neurogenic factors. When carbon dioxide was added to the oxygen-poor gas mixture in order to produce a relatively constant partial pressure of carbon dioxide in the hypoxic patient, the vascular resistance was not appreciably altered. This indicated that the fall in vascular resistance in the forearm during hypoxia was due more to the hypocapnia resulting from the hyperpnea than directly to the hypoxia itself.

KARPMAN

Fishman, A. P., Turino, G. M., Brandfonbrener, M., and Himmelstein, A.: The "Effective" Pulmonary Collateral Blood Flow in Man. J. Clin. Invest. **37**: 1071 (July), 1958.

This study of respiratory physiology was based on observations in 12 subjects with some anatomic basis for a pulmonary collateral circulation. These included subjects with prolonged obstruction of a pulmonary artery, unilateral pulmonary disease, so that 1 lung was perfused both by mixed venous blood and systemic arterial blood, and congenital absence of a normal pulmonary artery so that both lungs were perfused by systemic arterial blood. By a special adaptation of the Fick principle, it was found in subjects with bronchiectasis and cystic disease of the lungs that precapillary communications existed. Evidence of "effective" collateral blood flow was demonstrated in a subject with long-standing pulmonary arterial ligation. No effective collateral flow could be measured in subjects with either primary carcinoma of the lung or short-term pulmonary artery obstruction. Patients with atresia of the main pulmonary artery displayed large effective pulmonary collateral blood flows. These observations, discussed in detail in the text, emphasized the distinction between "effective" and total pulmonary collateral blood flow.

WAIFE

Lewis, B. M., Lin, T., Noe, F. E., and Komisaruk, R.: The Measurement of Pulmonary Capillary Blood Volume and Pulmonary Membrane Diffusing Capacity in Normal Subjects; the Effects of Exercise and Position. J. Clin. Invest. **37**: 1061 (July), 1958.

The diffusing capacity of the lungs for carbon monoxide was dependent not only on the thickness and the area of the membrane between alveoli and capillaries, but also on the volume of blood in the capillaries and the rate at which this blood can react with carbon monoxide. In this study, an estimate of the capillary blood volume and diffusing capacity of the pulmonary membrane in 19 normal subjects was studied. In addition, the effect of exercise and alterations in body position was examined. Under the conditions of the experiment described, both capillary blood volume and membrane diffusing capacity were significantly correlated with the weight, height, body surface area, vital capacity, and apparent diffusing capacity for carbon monoxide. The capillary blood volume appeared to be stable and reproducible over a long period of time (months) although the membrane-diffusing capacity was variable. In 4 subjects, these 2 parameters increased on mild exercise. Changing from the seated to the recumbent position caused changes in the capillary volume but not in the diffusing capacity. The observations seemed to fit in best with the hypothesis that the capillaries were incapable of dilatation and were either open or completely closed with only a small fraction of the alveolar capillaries open at any one time.

WAIFE

Maxwell, G. M., Castillo, C. A., White, D. H., Jr., Crumpton, C. W., and Rowe, G. G.: Induced Tachycardia: Its Effect upon the Coronary Hemodynamics, Myocardial Metabolism and Cardiac Efficiency of the Intact Dog. J. Clin. Invest. **37**: 1413 (Oct.), 1958.

Clinical supraventricular tachycardia was simulated in 9 intact anesthetized dogs in whom catheters were introduced into the pulmonary artery,

coronary sinus, and right atrium while an indwelling needle was placed in the femoral artery. Tachycardia was induced by direct electric stimulation of the right atrial wall through a wired catheter, so that the average heart rate rose from 92 to 193 beats per minute. During the period of tachycardia, which averaged 25 minutes per animal, it was found that the cardiac output was unchanged and the measured parameters of general metabolism remained stable save for a slight rise in oxygen consumption. Pulmonary artery pressure and thus pulmonary artery resistance plus right ventricular work rose, although femoral artery pressure and its reflected left ventricular work were unchanged. During tachycardia the coronary blood flow per minute rose significantly, as did the cardiac metabolic rate, as measured by oxygen consumption and carbon dioxide production. Calculated myocardial efficiency fell during the period of stimulation and it was therefore assumed that at the faster rates energy was inadequately converted to useful work.

FREEDBERG

Love, W. D., and Burch, G. E.: A Simple New Method for Estimating Cardiac Output. J. Lab. & Clin. Med. **52**: 515 (Oct.), 1958.

Cardiac output was measured in 14 anesthetized dogs using continuous intravenous fusion of rubidium^{86} and applying the Fick principle. Serial blood specimens were taken from the pulmonary artery, superior vena cava, the inferior vena cava above the liver and hepatic vein, a renal vein and the inferior vena cava distal to the kidneys. The total Rb^{86} content of each lung, the heart, the kidneys, and the organs of the portal bed was determined by digestion of the tissue. Cardiac output was calculated from the amount of isotope taken up by the tissues and the arterial venous difference in the plasma radioactivity. Five dogs in this series served as controls in that cardiac output was measured by the Stewart and Hamilton method employing T1824. It was found that cardiac output could be predicted with a mean relative error of less than 10 per cent of the Rb^{86} concentration which was reached in the arterial plasma during the infusion. The average plasma flow to any organ or tissue except the brain could be measured by obtaining a representative venous specimen and measuring its total Rb^{86} content at the time of sacrifice. The relationship between plasma Rb^{86} concentration and cardiac output in dogs was applied to the data from a group of human subjects given infusions of isotope previously. The mean value for cardiac output obtained in the patients without heart disease was 2.53 L./M.^{2}/min.

MAXWELL

Verzeano, M., Webb, R. G., Jr., and Kelley, M.: Radio Control of Ventricular Contraction in Experimental Heart Block. Science **128**: 1003 (Oct. 24), 1958.

Heart block was created in the dog by sectioning the bundle of His in the vicinity of the atrioventricular node and a miniaturized radio receiver, connected by wires to the myocardium, was placed beneath the musculature of the animal's thoracic wall. A radio-frequency field was set up around the cage in which the animals were kept, and it was found possible to stimulate the myocardium by such remote stimulation for periods as long as 8 days following surgery. The method was designed to limit the infection, discomfort, and limitation of motion that followed direct connection of a pulse generator to the myocardium via wires passing through the chest wall.

FREEDBERG

PULMONARY DISEASES

Amos, J. A. S.: Thrombosis of the Major Pulmonary Arteries. Brit. M. J. **II**: 659 (Sept. 13), 1958.

The findings were described in 19 patients in whom thrombosis of the major pulmonary arteries was confirmed at autopsy. There was a wide variety of predisposing illness and varied factors in pathogenesis. In 8 patients thrombosis was consequent on previous pulmonary embolism, in 9 the finding suggested that autochthonous thrombosis had occurred. In 2 patients the pathogenesis was not established with certainty. The clinical findings were extremely variable, at times minimal and at times those of sudden intractable right heart failure. The most frequent clinical course was that of repeated embolic episodes or of an overwhelming acute cor pulmonale. Only 1 patient showed a slowly progressive chronic cor pulmonale. The condition may first be suspected by roentgenogram. Examination of the chest may reveal right-sided heart enlargement, dilatation of the pulmonary artery proximal to the obstruction with alteration of the vessel contour and increased translucency of the lung fields distal to the obstruction. There may also be accentuation of the vessel outline due to diminished pulsations of the affected area. In the electrocardiogram the change from left-axis to right-axis deviation may be observed. By use of angiocardiography, obstruction to the major arteries has been demonstrated. Because of the varied clinical picture thrombosis of the pulmonary arteries should be considered in the diagnosis of any case of acute, subacute, or chronic cor pulmonale.

KRAUSE

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Keeler, R., and Schnieden, H.: Investigation of Mechanisms of Diuresis Produced in the Rat by an Intravenous Infusion of Isotonic Solution of Sodium Chloride. Am. J. Physiol. **195**: 137 (Oct.), 1958.

The intravenous infusion of isotonic saline produced a marked increase in the tubular rejection fractions for sodium and water. The glomerular filtration rate was slightly increased. The expansion of plasma volume produced by 6 per cent albumin in isotonic saline solution was less effective in producing a diuresis than a similar expansion of plasma volume by isotonic saline alone. These observations indicated that expansion of plasma volume alone cannot explain all the effects observed in saline diuresis. Bilateral vagotomy or bilateral severance of the cervical cardiac branches of the vagus did not significantly affect the diuretic response to intravenous isotonic saline.

KAYDEN

Perlmutt, J. H. and Olewine, D. A.: Alteration of Renal Response to Carbonic Anhydrase Inhibitor by Synthetic Adrenal Steroids. Am. J. Physiol. **195**: 142, (Oct.), 1958.

The increased urinary sodium output induced by acetazolamide in water-loaded adrenalectomized rats was partially antagonized by the mineralocorticoid, desoxycorticosterone glucoside, the increased potassium excretion was augmented and urine volume was not affected. Intact rats subjected to the same treatment showed only a small rise in potassium excretion. The glucocorticoid, hydrocortisone hemisuccinate, under the same conditions, elevated sodium, potassium, and water excretion in the adrenalectomized rats receiving acetazolamide; intact rats showed an increase of sodium and water excretion with no significant change in potassium output. Hydrocortisone hemisuccinate (2.5 mg.) alone increased water excretion in adrenalectomized rats to a slightly greater extent than acetazolamide alone, with considerably less sodium loss.

KAYDEN

Bricker, N. S., Stokes, J. M., Lubowitz, H., Dewey, R. R., Bernard, H. R., and Hartroft, P. M.: Experimentally Induced Permanent Unilateral Renal Disease in Dogs. J. Lab. & Clin. Med. 52: 571 (Oct.), 1958.

Unilateral renal disease was induced in dogs by producing total unilateral renal ischemia for 30 minutes followed by perfusion for a 10-minute period with 100 ml. of isotonic saline containing an aminonucleoside (6-dimethylaminopurine-3-amino-D-ribose), which was prevented from entering the systemic circulation by draining the renal vein. Split function studies were done before and after the procedure, facilitated by a preliminary bladder splitting surgical procedure with catheter drains to the outside from each hemibladder. A moderate to severe decrease in function of the experimental kidney was noted in all the animals. Depression of renal function was maximal in the period immediately following the experimental procedure followed by a limited increase in function over a period of 6 to 8 weeks, after which clearance values tended to stabilize at levels appreciably below the control values. There was no persistent proteinuria, indicating that the lesion produced was different from the nephrotic syndrome that can be induced in rats by the subcutaneous administration of this agent. Anatomically, decrease in renal mass occurred and microscopically dilatation and atrophy of tubules, tubular luminal casts, interstitial fibrosis, decrease in size of glomerular tufts, dilatation of Bowman's space, and thickening of the glomerular capsular epithelium and basement membranes were noted. The contralateral kidney remained normal and only minimal elevation of plasma urea and creatinine levels was seen to occur.

MAXWELL

Maluf, N. S. R.: Internal Diameter of Renal Artery and Renal Function. Surg., Gynec. & Obst. **107**: 415 (Oct.), 1958.

The diameter of the renal arteries was measured from translumbar aortograms in more than 59 patients having a variety of urologic conditions. A normal value (6.6 mm.) was found in advanced hydronephrosis due to acute uretral obstruction, in some instances of intermittent hydronephrosis and infrequently in other disorders. However, renal artery narrowing was regularly associated with reduced function of that kidney, and this was corroborated by pallor or absence of the instantaneous nephrogram. In prolonged hydronephrosis the narrowing consisted principally of intimal proliferation. This method was advocated for evaluating the function of each kidney when retrograde pyelography was not possible or feasible and in certain other situations involving bilateral renal damage.

ROGERS

Magid, G. J., and Forsham, P. H.: Clinical Studies on the Diuretic Effect of Chlorothiazide. Metabolism **7**: 589 (Sept.), 1958.

The properties of chlorothiazide and the mechanisms by which it affects urinary electrolyte and water excretion in man were studied in

16 hospitalized patients, 19 out patients, and 1 normal control subject. Natruresis was maximal within the first 2 hours after 1,000 mg. and lasted from 8 to 10 hours. The loss of chloride in the urine followed that of sodium; potassium excretion was much smaller. Bicarbonate excretion, measure of carbonic anhydrase-inhibiting activity of chlorothiazide, delayed in onset and gradually increased with dosage but was minimal at all doses. Three diuretics were compared with regard to their effect on the urinary electrolyte picture induced by α-fluorohydrocortisone. The mercurial produced a urine of greater volume which was more hypotonic with respect to sodium. There was a prompt but only partial reversal of the salt-retaining effect of the steroid by chlorothiazide as well as the others. The ionic pattern of excretion of chlorothiazide fell between that of acetazolamide and meralluride. In 3 edematous patients, the addition of acetazolamide potentiated the diuretic effect of chlorothiazide. Diuretic effects were shown in congestive heart failure, premenstrual edema, nephrosis, and cirrhosis. In the latter, an increase in blood ammonia may be a complication.

KURLAND

Chesley, L. C., Valenti, C., and Rein, H.: Excretion of Sodium Loads by Nonpregnant and Pregnant Normal, Hypertensive, and Pre-Eclamptic Women. Metabolism 7: 575 (Sept.), 1958.

The renal response to an infusion of 800 ml. of 3 per cent sodium chloride was studied in 17 nonpregnant women, 11 normal pregnant women, 13 women with pre-eclampsia, and 12 with essential hypertension. The mean inulin clearance of normal pregnant women was higher than that of nonpregnant women; the inulin clearance in pre-eclampsia was depressed compared to normal pregnancy. The average filtration rates were not changed significantly during and after infusion of hypertonic saline. In the first 2 hours following saline infusion, the sodium excretion in pre-eclamptic women was significantly depressed compared to nonpregnant and normal pregnant women. The sodium clearances in nonpregnant and normal pregnant women did not differ before or after salt loading; those of pre-eclamptic women were significantly lower in control periods and during and after salt loading. At comparable filtered loads, sodium clearance was markedly lower in pre-eclamptic and hypertensive women as compared to normal subjects. A larger percentage of filtered sodium was reabsorbed in women with pre-eclampsia than in normal women. It was concluded that renal tubular activity was markedly altered in women with pre-eclampsia and, in lesser degree, in pregnant women with hypertensive disease.

KURLAND

RHEUMATIC FEVER

Costero, I., Barroso-Moguel, R., Chevez, A., Monroy, C., and Contreras, R.: The Lesions of Rheumatic Fever in Patients Treated with Cortisone. II. The Most Frequent Visceral Localizations. Arch. Inst. Cardiol. Mexico 28: 294 (May-June), 1958.

The endomyocardial changes seen at autopsy in patients who had rheumatic disease and had been treated with cortisone have been described in a previous article. The changes found in other organs frequently involved in rheumatic disease are reported. The incidence of fibrinous pericarditis was not influenced by the treatment; necrosis was more frequent and more extensive; the healing process was slow, the fibroblastic reaction more intense, the newly formed connective tissue was looser. The inflammatory infiltrates of lymphoid cells, in the heart and also in other organs, were not influenced by cortisone. Rheumatic pneumonitis was found more frequently in patients treated with corticoids (37 per cent versus 11 per cent in patients not treated with corticoids); the fibrinoid necrosis of the alveolar septa was more extensive and the organization of the exudate was slow. Only 1 instance of rheumatic encephalopathy was found in this series of 30 patients; no detailed study of the cerebral pathology was therefore presented, and it was tentatively concluded that cortisone had a favorable effect on this localization, as on the polyarthritic manifestations of the rheumatic disease. Renal lesions were described in 4 patients, mild in 2, moderate in 1, and severe in 1; similar changes have not been found in other instances of rheumatic fever; it was inferred that these changes were due to the rheumatic process, and were made manifest by the corticoid treatment.

CALABRESI

ROENTGENOLOGY

Porstmann, W., Geibler, W., and Wolf, W.: Retrograde Angiocardiography of the Left Heart Combined with Measurement of the Intracardiac Pressures. Fortschr. Röntgenstr. 89: 397 (Oct.), 1958.

In 17 patients 4 to 53 years old the left ventricle was catheterized through the right common carotid artery with a fairly stiff catheter guided carefully through the aortic valves in systole, under control of the fluoroscopic image amplifier.

Location of the catheter tip in the free lumen of the ventricle was verified by the contour of the intraventricular pressure pulse and the absence of ventricular extrasystoles. Injection of up to 60 ml. Triopac 400 (1 ml./Kg.) in 1 to 2 seconds allowed exact visualization of the aorta, the left ventricle and its valves, and the coronary arteries, and exact determination of mitral regurgitation and left-to-right shunts. Pressure recording while the catheter was pulled back from the ventricle revealed tracings typical for various types of aortic valvular disease. Only one complication (cerebral embolism with hemiparesis) was observed; but as the patient had mitral disease, this was not necessarily caused by the catheterization.

LEPESCHKIN

Ohara, I., and Tanno, A.: Abnormal Mediastinal Shadows Caused by the Tortuous Thoracic Aorta. Am. J. Roentgenol. **80**: 231 (Aug.), 1958.

Mediastinal tumors can now be operated upon with a low mortality. The most common cause of mediastinal enlargement by large vessels was long thought to be due to aneurysm of the aorta or aortitis. Now it appeared that coaretation and kinking of the aorta (pseudo-coaretation) also enlarged the mediastinal shadow. Three cases of dilatation and elongation of the thoracic aorta causing rounded mediastinal shadows were presented. A diagnosis of mediastinal tumor was seriously considered in all 3. Conventional roentgenographic procedures were carried out, but of these studies posteroanterior roentgenography with higher voltages and laminography was most helpful in establishing that the aorta caused the abnormal shadows. It appeared that attention should be paid to possible blood vessel abnormalities when interpreting mediastinal masses on conventional roentgenograms.

KITCHELL

Edling, N. P. G., Helander, C. G., Persson, F., and Asheim, A.: Renal Function after Aortography with Large Contrast Medium Doses. An Experimental Study in Dogs. Acta radiol. **50**: 351 (Oct.), 1958.

This investigation indicates that the injection of large doses (40-80 ml.) of contrast medium (Urografin 60 per cent, Miokon 50 per cent) into the aorta of anesthetized, healthy dogs just above the origin of the renal arteries does not cause any renal abnormalities. Renal function was tested by means of inulin and PAH clearances several days before and after the contrast material injection, and the kidneys were also examined histologically. The volume of contrast medium injected was relatively 5 times as large as that injected into the human aorta, and the authors concluded that properly performed aortography will not damage healthy kidneys in human subjects. The renal damage that has been described in the literature was attributed to the injection of an aortic dose of contrast medium directly into a renal artery, and to the performance of aortography in patients with impaired kidney function.

PAUL

McFall, R. A., Dowdy, A. H., and O'Laughlin, B. J.: Reaction of the Heart to Selective Angiocardiography. Am. J. Roentgenol. **80**: 394 (Sept.), 1958.

Although angiocardiography is a well accepted procedure, selective angiocardiography is still in the process of evaluation. Clinical and experimental evidence presented here gave no support to apprehensions concerning this procedure. The methods, difficulties, and cautions in performing selective angiocardiography were discussed. The newer contrast media employed seemed less toxic than previous materials used. Radiation damage was not remarkable. The procedure was a reproducible one with diagnostic and surgical promise and the authors reported 159 human cases performed without fatality or significant sequelae.

KITCHELL

Young, B. R., Funch, R. B., MacMoran, J. W., Stauffer, H. M., and Oppenheimer, M. J.: Ultrashort (Millisecond) Timing in Roentgen Diagnostic Procedures Including Angiocardiography: Comparison of Dynapulse and Impulse Timing. Am. J. Roentgenol. **80**: 375 (Sept.), 1958.

Experience with the dynapulse method of ultra-fast roentgen-ray timing, with exposures as short as 1/1000 second, showed that this method was of practical value for the production of sharp roentgenograms in pediatric roentgenography, especially in angiocardiography. Such millisecond exposures stopped motion of 80 cm. per second, which approached the estimated maximal rate of blood flow. Dynapulse timing, however, revealed no diagnostic superiority over rapid impulse timing in pediatric chest roentgenography, in cerebral angiography, and in angiocardiography in normal dogs.

KITCHELL

Poker, N., Finby, N., and Steinberg, I.: The subclavian Arteries: Roentgen Study in Health and Disease. Am. J. Roentgenol. **80**: 193 (Aug.), 1958.

Roentgen studies over the last 20 years have resulted in considerable data regarding the sub-

clavian arteries in health and disease. Following angiocardiography all vascular trunks arising from the aortic arch are opacified. The right subclavian artery was seen in its entirety in the frontal projection while the first portion of the left subclavian artery was best seen in the left anterior oblique view. Such conditions as anomalous origin, congenital subclavian arteriovenous fistula and aneurysm, subclavian buckling, occlusion (Takayusu's disease), tumor involvement and aneurysm were demonstrated. Conditions caused by the presence of coarctation of the aorta, the thoracic inlet syndrome, and kyphoscoliosis can be discovered. The authors seek to establish normal standards of caliber and length for the subclavian arteries and present data of academic and practical significance concerning the subclavian arteries in health and disease.

KITCHELL

Laconi, A., and Zaccone, G.: Analytic Roentgen Kymography of the Normal Cardiac Cycle. Am. J. Roentgenol. **80**: 248 (Aug.), 1958.

In 1929 Cignolini began investigating the analytic roentgen kymograph (ARK). This first kymograph was improved to meet the following requirements: study of the cardiac cycle at the rate of 0.01 second, simultaneous registration at different points, and registration of several cardiac cycles on the same film. In 1950 Cignolini designed a new apparatus called the polykymograph, which provided for the ARK and the plane roentgen kymograph (RK) to be made on the same film. The new polykymograph permits registration of ARK and RK on the same film, lessening of total load on the roentgen tube, greater detail, easy and rapid use with precision of registration, and registration of simultaneous electrocardiograms and other graphic representations of the cardiac mechanical cycle. Studies done with this method were described and normal ventricular, atrial, and vascular patterns were discussed.

KITCHELL

SURGERY AND CARDIOVASCULAR DISEASE

Dye, W. S., Julian, O. C., Javid, H., Grove, W. J., Morehead, D. E., and Prec, O.: Aortic Commisurotomy Under Direct Vision. Ann. Surg. **148**: 469 (Sept.), 1958.

A series of 23 patients who had surgical treatment of the aortic valve under direct vision using hypothermia and inflow occlusion was presented. All the patients (except those with congenital aortic stenosis) had significant cardiac symptoms placing them in class III or class IV. The ages of the patients ranged from 5 to 56 years. In 18 patients with calcific stenosis, 9 have shown considerable improvement and 4 died—3 operative deaths and 1 late death. Of the 5 congenital cases it was more difficult to evaluate improvement; none in this group died.

SAGALL

Winter, W. R., Carmichael, D. B., Baronofsky, I. D., and Baker, W. S., Jr.: Cardiac Surgery Associated with Pregnancy. Am. J. Obst. & Gynec. **76**: 572 (Sept.), 1958.

With improved control of infection, toxemia of pregnancy and hemorrhage, heart disease has gained a prominent place as a primary cause of death of the parturient woman. With rapid advances noted in the field of cardiac surgery, it is important that specific correctible cardiac lesions be recognized early so that more of these patients may be salvaged and the maternal mortality due to heart disease be reduced. Among the 37 patients included in this report 8 were pregnant at the time of operation, 2 had coarctation of the aorta, and 6 had mitral stenosis. Those with coarctation were delivered of normal infants without difficulty following repair of the lesion. Of those undergoing mitral commissurotomy, 1 died during operation, 1 had a premature delivery 9 weeks after operation, and 1 delivered a mongoloid infant. Operation prior to the twenty-eighth week of pregnancy was advised in selected cases of mitral stenosis and in coarctation of the aorta. Pregnancy was not considered a contraindication for surgery and did not appear to affect the fetus adversely or to increase the incidence of prematurity under the protective influence of progestational hormone therapy. Therapeutic abortion for pregnant patients with mitral stenosis is becoming an obsolete method of management as a result of the success noted with mitral commissurotomy in indicated cases and conservative management in the remainder.

SHUMAN

VALVULAR HEART DISEASE

Glenn, F., and Redo, S. F.: Mitral Stenosis and Gallstones. Ann. Surg. **147**: 812 (June), 1958.

In a group of young women between the ages of 26 and 45, operated upon for mitral stenosis, an unusually high incidence of gallstones was found. In many this was evidenced by attacks of cholecystitis occurring in the immediate postoperative period following commissurotomy. Because of this high frequency of the 2 conditions in young women and also because of the problems in differential diagnosis that may arise in the postoperative period between acute cholecystitis and right heart failure in these patients, the

authors have formulated a policy of instituting x-ray studies of the gallbladder in all sick patients prior to mitral surgery, even in the absence of symptoms referable to the biliary tract. They further believe that unless the indications for the surgical correction of the mitral stenosis are most urgent biliary tract disease if present should be operated upon first. In their experience cholecystectomy alone or combined with common duct exploration has been well tolerated by patients with moderately severe mitral stenosis and the mitral lesion can then be corrected in 3 weeks or more.

SAGALL

Black, H., and Harken, D. E.: Mitral Valvuloplasty in Patients Past Fifty. New England J. Med. **259:** 361 (Aug. 21), 1958.

A group of 154 patients with mitral stenosis who were between the ages of 50 and 70 at the time of operative correction of the lesion were compared with a larger group of younger patients. As would be expected a higher percentage of the older patients were in an advanced stage of their disease (group IV cases). Similarly, preoperative arterial embolization, associated arteriosclerotic heart disease, and elevated blood pressure were all significantly more common in the older age group. Despite these adverse factors, no significant increase in operative risk was found with advancing age when similar stages of the disease were compared. Evaluation after an average of 25.7 months further revealed in this comparison that the frequency of late death and the percentage of improvement after operation in the group of older patients was practically identical with that found at younger ages. On the basis of these observations the authors conclude that the properly selected patient over the age of 50 who has mitral stenosis should be offered surgical relief with the same assurance that is justified at an earlier age.

SAGALL

Goldberg, H., Smith, R. C., and Raber, G.: Estimation of Severity of Aortic Stenosis by Combined Heart Catheterization. Am. J. Med. **24:** 853 (June), 1958.

Simultaneous left and right heart catheterization was performed to measure pressure-flow relationships in 37 patients with clinically pure aortic stenosis. The most constant physiologic abnormality was a pressure gradient between the left ventricle and the aorta. This gradient was dependent not only upon the degree of obstruction but upon the rate of flow. No correlation could be made between the contour of the tracheal artery pressure tracing and the degree of obstruction. In all patients, the aortic orifice was below 1.1 cm.^{2} Left ventricular function was altered with reduction generally of cardiac output. Systolic and end-diastolic pressures in the left ventricle were elevated and total work was increased. The mean left atrial pressure was elevated, reflecting the high left ventricular diastolic pressure, possibly a result of myocardial failure or the decreased distensibility of hypertrophy.

KURLAND

Jürgens, R., Stecken, A., and Witte, H.: Clinical Significance of Roentgenologic Findings of Left Atrial Mural Calcification. Fortschr. Geb. Röntgenstr. **88:** 534 (May), 1958.

Mural calcification of the left atrium was found in 4 of 180 patients with mitral stenosis; this was most clearly seen in the oblique view, in roentgenkymograms and especially in tomograms. In agreement with 38 cases from the literature, it was seen only in mitral stenosis of long duration with atrial fibrillation, accompanied by significant mitral insufficiency and multivalvular involvement. In most cases this finding constitutes a contraindication to mitral valvulotomy.

LEPESCHKIN

VASCULAR DISEASE

Peacock, J. H.: Aetiological Factors in Primary Raynaud's Disease. Brit. M. J. **2:** 825 (Oct. 4), 1958.

Primary Raynaud's disease implies intermittent attacks of digital pallor or cyanosis with no known local cause or associated systemic disease. Twenty-one patients with this disease were discussed. In 16 of the 20 patients in whom a complete family history was available a history of similar attacks was present in one or both parents. It was reasonable to assume an inheritable predisposition, although the nature of the inherited defect remained unknown. In 8 patients symptoms arose within 6 months of childbirth; in 6 patients digital symptoms appeared after the onset of menopause; and in 7 patients the symptoms followed a period of prolonged and severe mental stress. This group of 21 cases represented 50 per cent of a larger series in the remainder of which no such etiologic factor could be detected.

KRAUSE

DeBakey, M. E., Crawford, E. S., Cooley, D. A., and Morris, G. C., Jr.: Surgical Considerations of Occlusive Disease of the Abdominal Aorta and Iliac and Femoral Arteries; Analysis of 803 Cases. Ann. Surg. **148:** 297 (Sept.), 1958.

An analysis of the surgical treatment of 803 cases of occlusive disease of the aorta and fem-

oral arteries was presented. This series thoroughly established the concept that in chronic arteriosclerotic occlusive disease of the lower extremities the obstructing lesion was usually well localized and segmental in nature with a relatively patent lumen above and below the occluding lesion. The cases could be classified into 2 major groups, namely, aorto-iliac occlusion and femoral occlusion. The series of aorto-iliac occlusion comprised 448 patients of whom 100 (44 per cent) showed complete aortic occlusion and 249 (56 per cent) an incomplete aortic occlusion. Associated occlusive disease of the peripheral arterial bed was found in 18 per cent. Three types of surgical procedures were employed in these patients depending on the location, extent, and nature of the occlusive process as well as certain systemic factors. These consisted of thromboendarterectomy, excision with graft replacement, and bypass graft. With associated peripheral disease lumbar sympathectomy was considered a desirable supplemental procedure. In about 95 per cent of the patients a pulsatile circulation through the major arterial channel was restored by employing the technic indicated in that case. The operative mortality was 2.7 per cent and resulted primarily from associated cardiac and renal disease. Nine late deaths, due primarily to cardiac disease, occurred from 1 to 30 months after discharge from the hospital. Recurrent occlusion occurred in only 8 patients after varying periods following operation ranging from 3 to 27 months. With occlusive disease of the femoro-popliteal region wide variations in the nature and extent of the pathologic features of the occlusive process were found, but the cases could be classified into 3 main groups: (1) those with a discrete localized occlusive lesion with relatively normal arteries above and below the occlusion, (2) those with more extensive involvement of the femoral artery but with patency of the popliteal and distal arterial bed, and (3) those with still more extensive and diffuse obliterative disease extending well down into the smaller vessels of the calf. Preoperative arteriographic studies were necessary to determine the form of the occlusion and the application of the appropriate surgical procedure. Only those patients in the first 2 groups could be helped by surgical procedures which aimed at restoring normal circulation while those in the third group were best treated by lumbar sympathectomy. Of the 353 cases of occlusive disease of the femoral artery in this series 90 per cent were treated by means of bypass graft. Endarterectomy was still considered a desirable procedure but its use was limited only to those patients in the first group. In 84 percent of all the treated cases a normal pulsatile circulation was restored. Recurrent occlusion was observed in only 14 per cent of cases ranging over a period of 3 weeks to 38 months after discharge from the hospital.

SAGALL

Crevasse, L. E., and Logue, R. B.: Carotid Artery Murmurs. J.A.M.A. **167:** 2177 (Aug. 30), 1958.

The clinical syndrome of carotid artery thrombosis is well recognized. However, obstruction of the carotid artery without occlusion is more common and is generally unrecognized. Such occlusion produces localized carotid murmurs which can be detected by auscultation of the head and neck. In unselected hospital patients, 7 per cent showed carotid systolic murmurs and 2 per cent showed continuous murmurs indicative of partial occlusion of the carotid artery. A continuous murmur over the carotid bulb is a valuable sign of carotid artery insufficiency and may be found in completely asymptomatic patients with unsuspected carotid artery insufficiency as well as in patients in whom the diagnosis of "cerebral thrombosis" has been entertained. It also may be found in patients in whom transient neurologic symptoms have appeared, usually in relation to changes in blood pressure. Carotid artery insufficiency is treatable by both surgery and anticoagulant therapy and its early recognition and treatment before a complete thrombosis occurs are important.

KITCHELL

Livingstone, P. D., and Jones, C.: Treatment of Intermittent Claudication with Vitamin E. Lancet **2:** 602 (Sept. 20), 1958.

The value of vitamin E in the treatment of peripheral vascular disease was studied in 40 nondiabetic male patients with obliterative vascular disease who complained of intermittent claudication. Patient evaluation and exercise tolerance were measured in 20 patients treated with vitamin E and in 20 with placebo. Thirteen treated patients showed subjective and objective improvement as compared with only 2 in the control group. No criteria were formed for selection of suitable cases for vitamin E therapy, but large doses over long periods were necessary, for there was a considerable delay before any response.

KURLAND

Carral, F., and Soto, C. A.: Abdominal Venous Thrombosis in the Adult Cardiac. Arch. Inst. Cardiol. México **28:** 333 (May-June), 1958.

In a total of 1,597 autopsy reports, 67 instances of thrombosis of the abdominal veins were found: 44 of these were limited to the pelvic vessels, 7

involved the iliac veins and did not extend to the visceral veins. Of the 16 remaining cases, 11 were cardiac patients; 6 of these also had thrombosis of the right cardiac chambers. Seven of these 16 patients were not suitable for detailed analysis and clinicopathologic correlation. Of the 9 specimens studied, 6 had unilateral or bilateral renal vein thrombosis, 2 had isolated splenic, 1 had splenic and portal, and 1 had isolated portal vein thrombosis. Three cases of acute renal vein thrombosis had evidence of a nephrotic syndrome; the 1 instance of chronic renal vein thrombosis also had nephrosis, recurrent abdominal pain, and late transitory arterial hypertension. While in children massive infarction and hematuria were noted, these patients had only moderate or noncharacteristic hematuria, and hemorrhagic infarction was not found at autopsy. None of the patients with portal or splenic thrombosis has had gastric hemorrhages; the patient with portal and splenic thrombosis had hemorrhagic infarction of the liver.

CALABRESI

Sheps, S. G., Spittel, J. A., Jr., Fairbairn, J. F., II and Edwards, J. E.: Aneurysms of the Splenic Artery with Special Reference to Bland Aneurysms. Proc. Staff Meet., Mayo Clin. **33**: 281 (July 23), 1958.

Aneurysms of the splenic artery are uncommon. In a 47-year period, ending in December 1957, 46 aneurysms were found in the course of 28,512 postmortem examinations, an incidence of 0.16 per cent. Sixty-eight per cent occurred in women. Most of the lesions in both sexes afflicted persons in the sixth, seventh and eighth decades. Three (6 per cent) ruptured and were the cause of death. The spleen was enlarged in 11 patients. In 5 patients (21 per cent) aneurysms were found elsewhere in the body; 3 of these latter lesions affected intracranial arteries. Twenty-four aneurysms were asymptomatic and were not suspected clinically. Two of the aneurysms were mycotic and were associated with subacute bacterial endocarditis. Two dissecting aneurysms were restricted to the splenic artery. One of these had developed in continuity with acute hemorrhagic pancreatitis and the other was associated with multiple systemic embolization. Of the remaining 20 bland aneurysms, 11 were congenital and 7 of these were associated with secondary deposits of atheroma.

KRAUSE

Starer, F., and Sutton, D.: Aortic Thrombosis. Brit. M. J. **1**: 1255 (May 31), 1958.

Aortic thrombosis (Leriche's syndrome) was studied in 32 patients over a 4-year period. Although the autopsy incidence is approximately 0.12 to 0.15 per cent, the clinical incidence is closer to 0.61 per cent. The clinical diagnosis in all patients in this study was confirmed by aortography. There were 24 males and 8 females. The average age for the group was 51.3 years. Twenty patients had a gradual onset of symptoms and in 12 patients the onset was more rapid. The chief symptom was intermittent claudication and usually this was progressive in nature. In 50 per cent of the cases this was associated with a loss of power in the muscles of the legs and also wasting of these muscles. The most important sign of aortic thrombosis was the loss of palpable arterial pulsations below the block. However, the absence of femoral pulsations does not imply that these vessels must be occluded, for it has been proved by aortography that this can be due to the damping of the pulse where blood is carried by collateral vessels from the aorta to the femoral arteries. A less often observed sign of aortic thrombosis is vigorous pulsation above the site of block. A systolic murmur over the spinous processes of the lumbar vertebrae and lower abdomen due to the development of collateral circulation can occur. A plain roentgenogram of the involved site is of no help, and even the identification of calcification means little in the diagnosis of aortic thrombosis. The most helpful diagnostic air is aortography and a certain diagnosis includes the visualization of an abruptly ending column of contrast medium. Usually the block lies between the level of the renal arteries and the aortic bifurcation, and collateral blood vessels are often demonstrated. Although in this series there were practically no complications to the aortography, the authors recognize that the procedure is not innocuous. Furthermore, false positive x-rays may be due to subintimal injection of the dye stuff and also extension of the thrombosis, anuria, and paraplegia have been reported as complications. The chief differential diagnosis is that of bilateral iliac thrombosis, which can usually be accomplished by aortography. Hypertension when associated with aortic thrombosis may in fact be due to blockade of a renal artery by retrograde extension. Impotence due to inadequate blood flow to the corpora cavernosa through the internal pudendal artery does occur. This symptom often is reversible when adequate collateral blood flow to the corpora cavernosa develops. It is the feeling of the authors that the prognosis is not as poor as previously thought in either the untreated or the treated form. Even though major surgery is available for aortic thrombosis, careful clinical judgment must be used in deciding whether this should be attempted.

KRAUSE

Keen, G., and Leveaux, V. M.: Prognosis of Cerebral Embolism in Rheumatic Heart Disease. Brit. M. J. **2**: 91 (July 12), 1958.

Cerebral embolism occurred in 34 (20 per cent) of 172 patients with rheumatic heart disease. The right and left cerebral hemispheres were involved with almost equal frequency. Hemiparesis was the resultant major disability, being severe in 10, moderate in 16, and mild in 6 patients. Of 33 patients analyzed, less than one fifth died within 3 months. Two thirds of the patients made a virtually full clinical recovery. The average time to the beginning of recovery was 1 week, and to maximum recovery, it was 4 months. Based on this data, the authors emphasized a hopeful outlook for patients with this complication of rheumatic heart disease as regards neurologic recovery.

KRAUSE

OTHER SUBJECTS

Sharpey-Schafer, E. P., Hayter, C. J., and Barlow, E. D.: Mechanism of Acute Hypotension from Fear or Nausea. Brit. M. J. **2**: 878 (Oct. 11), 1958.

Fear, often associated with nausea, may cause syncope. The fear of the dental chair and the nausea produced by the use of apomorphine in alcoholics were used to study the dynamics of such syncope. Continuous circulatory measurements were made before and during nitrous oxide anesthesia for tooth extraction. Five out of 21 dental patients developed acute hypotension with vasodilatation of the forearm vessels; 4 of these before the anesthetic was given. Fear appeared to be the main cause, with a fall in arterial oxygen saturation as a possible minor factor. Apomorphine-induced nausea caused a fall in the effective filling pressure of the heart which preceded hypotension and syncope. The authors suggested that emotional stimulation of the heart beat and a fall in cardiac filling pressure causes virtual emptying of a ventricular chamber during systole which fires the afferent mechanism of the faint reflex. Normally a person who faints, falls to the ground and the supine position increases the filling pressure of the heart with rapid recovery of consciousness. There is strong evidence that subjects with heart failure, whose ventricles are not easily emptied, do not faint.

KRAUSE

REVIEWS IN CARDIOVASCULAR DISEASE

Brun, C., and Raaschou, F.: Kidney Biopsies. Am. J. Med. **24**: 676 (May), 1958.

Berliner, R. W., Levinsky, N. G., Davidson, D. G., and Eden, M.: Dilution and Concentration of the Urine and the Action of Antidiuretic Hormone. Am. J. Med. **24**: 730 (May), 1958.

Pitts, R. F.: Some Reflections on Mechanisms of Action of Diuretics. Am. J. Med. **24**: 745 (May), 1958.

Sloan, A. W.: Cardiac Gallop Rhythm. Medicine **37**: 197 (Sept.), 1958.

Hirst, E. A., Jr., Varner, J. J., Jr., and Kime, S. W., Jr.: Dissecting Aneurysm of the Aorta: A Review of 505 Cases. Medicine **37**: 217 (Sept.), 1958.

von Euler, U. S.: Some Aspects of the Role of Noradrenaline and Adrenaline in Circulation. Am. Heart J. **56**: 478 (Sept.), 1958.

Kincaid, O. W., and Davis, G. D.: Abdominal Aortography. New England J. Med. **259**: 1017 (Nov. 20), 1958.

Brandenburg, R. O.: Symposium on Diagnostic Applications of Indicator-Dilution Curves Recorded from the Right and Left Sides of the Heart. Proc. Staff Meet., Mayo Clin. **33**: 535 (Oct. 29), 1958.

Edwards, J. E., and Burchell, H. B.: Pathologic Anatomy of Mitral Insufficiency. Proc. Staff Meet., Mayo Clin. **33**: 497 (Oct. 15), 1958.

August, J. T., Nelson, D. H., and Thorn, G. W.: Aldosterone. New England J. Med. **259**: 917 (Nov. 6), 1958.

August, J. T., Nelson, D. H., and Thorn, G. W.: Aldosterone (Concluded). New England J. Med. **259**: 967 (Nov. 13), 1958.

Elkington, J. St. C.: Cerebral Vascular Disease in the Light of Modern Techniques. Lancet **2**: 275 (Aug. 9), 1958.

Wood, P.: Pulmonary Hypertension with Special Reference to the Vasoconstrictive Factor. Brit. Heart J. **20**: 557 (Oct.), 1958.

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N.Y.
Telephone Gramercy 7-9170

NEW GRANTS-IN-AID AWARDS BRING AHA RESEARCH TOTAL TO $3,300,000 FOR YEAR

Grants-in-Aid totaling more than $1,750,000 have been made to 244 investigators under the national research support program of the American Heart Association and its affiliates for the 1959-60 fiscal year. These grants bring to 424 the number of national research awards made by the Association for 1959-60. Announced previously were awards of approximately $1,600,000 in fellowships and investigatorships to 180 scientists, including seven Career Investigators the Association supports on a lifetime basis.

The combined total of approximately $3,300,000 is the largest sum ever appropriated by the Association's National Office to support research in a single fiscal year. It represents a commitment of approximately 57 percent of the income received by the National Office from public contributions to last year's Heart Fund appeal and brings to more than $44,000,000 the total channeled into scientific research by the AHA and its affiliates since reorganization as a national voluntary health agency in 1948.

Additional research awards for 1959-60 will be made to scientists by affiliated state and local Heart Associations. Last year these totaled approximately $5,500,000, with an increase expected in the coming fiscal year.

A complete list of recipients of grant awards appears at the end of this section.

APPLICATIONS FOR AHA RESEARCH SUPPORT NOW BEING INVITED

The Association is now accepting applications from research investigators for support of studies to be conducted during the fiscal year beginning July 1, 1960.

September 15, 1959, has been set as the deadline for applying for Research Fellowships and Established Investigatorships. Applications for Grants-in-Aid must be made by November 1, 1959.

Applications may be made for awards in the following categories:

Established Investigatorships: Usually awarded for five years, subject to annual review, in amounts ranging from $6,500 to $8,500 yearly plus dependency allowance, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. In addition, a grant of $500 is made to the investigator's department to assist in defraying the expenses of his research program. Applicants for Established Investigatorships may apply for Grants-in-Aid to support their research at the same time they apply for Established Investigatorships.

Advanced Research Fellowships: Awarded for periods of one or two years to postdoctoral applicants who have had some research training and experience but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25 percent of their time in professional and scientific activities not strictly of a research nature, providing that these will contribute to their professional development and do not involve services for a fee. These stipends range from $4,600 to $6,500 annually. Additionally, a grant of $500 is made to the investigator's department as in the case of Established Investigators.

Research Fellowships: A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,800 to $5,700. However, this type of award is primarily made by local Heart Associations.

Grants-in-Aid: Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

Further information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

Six sessions of broad clinical interest under sponsorship of the Council on Clinical Cardiology will be included in the American Heart Association's 32nd annual Scientific Sessions, to be held at the Trade and Convention Center in Philadelphia, October 23-25. These clinical sessions will run concurrently with special scientific sessions and programs sponsored by other Councils of the Association at which original investigative work will be presented.

This year's program will also include a joint session with the American College of Cardiology, which is conducting its Interim Meeting to coincide with the AHA Scientific Sessions for the first time. The College has scheduled a dinner on Friday, October 23, to be followed by its popular "Fireside Conferences" in which Heart Association members will participate. On Sunday afternoon, October 25, the College will present a panel jointly with the Council on Clinical Cardiology on the subject of "Cardiac Resuscitation."

In addition, the Association's Council on Arteriosclerosis, formerly the American Society for the Study of Arteriosclerosis, will co-sponsor a symposium on "Conflicting Concepts of Atherogenesis" on Sunday morning and will participate in Sunday afternoon's program on arteriosclerosis. The new Council will hold its business and independent scientific meetings in Chicago, November 8-9, 1959.

Secretary Arthur S. Flemming of the U. S. Department of Health, Education and Welfare, will be guest speaker at a business luncheon of the Council on Community Service and Education on Saturday, October 24 at the Bellevue Stratford Hotel. Mr. Flemming will speak on "The Role of Voluntary Health Associations in Meeting Future Health Needs."

The Scientific Sessions program has been outlined tentatively as follows:

Friday, October 23:

A morning session on clinical cardiology will be devoted to a symposium on "Regulatory Mechanisms of the Cardiovascular System." Simultaneous morning sessions are scheduled on the subjects of rheumatic fever and congenital heart disease, and on circulation. The afternoon program includes: presentation of submitted papers of general interest in clinical cardiology; the Lewis A. Conner Memorial Lecture, to be given by Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago; a session on cardiovascular surgery.

Saturday, October 24:

A morning session on clinical cardiology will consist of two symposia: "Recent Developments in Diagnostic Techniques" and "Open Heart Surgery in Acquired Valvular Disease." Concurrently, a morning session will be held on high blood pressure research. Scheduled during the afternoon are: presentation of the Albert Lasker Award; the George E. Brown Memorial Lecture on "Circulatory Congestion and Heart Failure" by Ludwig W. Eichna, M.D., Professor of Medicine, New York University College of Medicine; a symposium on "Congestive Heart Failure," including a panel on "Treatment of Congestive Heart Failure" and a presentation "Life After Heart Failure;" a session on basic science; a session on cardiovascular surgery.

Sunday, October 25:

Included in the morning sessions are a panel on "Conflicting Concepts of Atherogenesis" and a concurrent session on "Instrumental Methods in Cardiovascular Research." In

addition to a panel to be conducted jointly with the American College of Cardiology during the afternoon, a concurrent session will be held on arteriosclerosis.

The program will include a session on medical motion pictures. Each film will be introduced by the author and will be followed by discussion. A section of scientific and industrial exhibits will also be included.

Following the Scientific Sessions, the 35th Annual Meeting of the Assembly, delegate body of the Association, will be held on October 26-27 in the Bellevue Stratford Hotel. Six Assembly panels will be in session all day Monday. They will discuss: Research; Fund Raising; Relationships and Responsibilities Between National, State and Local Heart Associations; Community Relationships of Heart Associations; Program Activities in Community Service and Education; and Heart Association Organization.

The general session of the Assembly meets on Tuesday morning to review panel recommendations and elect officers and Board members of the Association.

CARDIOLOGY MEETINGS SCHEDULED IN MEXICO

To celebrate the 15th anniversary of its founding, the National Institute of Cardiology of Mexico is sponsoring an International Symposium on Arteriosclerosis and Coronary Heart Disease, to be followed by the First Mexican Congress on Cardiology. The Symposium is scheduled for September 20-24; the Congress for September 25-26, both in Mexico City. The meetings are co-sponsored by the Mexican Society of Cardiology.

Outstanding cardiologists from various countries have been invited to report on their most recent investigations and clinical findings. Presentations will be translated simultaneously into Spanish, French and English. Registration fees are 100 *pesos* (approximately $8.00) for the Symposium, 50 *pesos* for the Congress. Additional information may be obtained from Dr. Manuel G. Noguera, Coordinator, National Institute of Cardiology, Av. Cuauhtemoc 300, Mexico, D. F.

LIFE INSURANCE FUND OFFERS FELLOWSHIPS, GRANTS

The Life Insurance Medical Research Fund is receiving applications for fellowship and grant awards effective July 1, 1960, as follows:

(1) Until October 15, for post-doctoral research fellowships. Candidates may apply for support in any medical science field. Preference will be given to those interested in fundamental problems, particularly cardiovascular function or disease. Minimum stipend is $4,500, with travel and dependency allowances.

(2) Until November 1, for grants to institutions in aid of cardiovascular research. Support is available for physiological, biochemical and other basic work and clinical research in the cardiovascular field. Information and application forms may be obtained from the Fund's Scientific Director, 345 East 46th Street, New York 17, N. Y.

MEETINGS CALENDAR

August 10-13: National Medical Association, Detroit. John T. Givens, 1108 Church Street, Norfolk, Va.

September 13-17: International College of Surgeons, U. S. Section, Chicago. Ross T. McIntyre, 1516 Lake Shore Drive, Chicago 10, Ill.

September 22-25: American Roentgen Ray Society, Cincinnati. C. A. Good, 200 First Street, S.W., Rochester, Minn.

September 28-October 2: American College of Surgeons, Atlantic City. Paul R. Hawley, 40 E. Erie Street, Chicago 11, Ill.

October 14-17: American College of Chest Physicians, Albuquerque, N. Mex. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N.Y.

November 2-4: Association of American Medical Colleges, Chicago. Ward Darley, 2530 Ridge Avenue, Evanston, Ill.

November 6-7: Central Society for Clinical Research, Chicago. A. S. Weisberger, 2065 Adelbert Road, Cleveland 6, Ohio.

November 8-9: American Heart Association's Council on Arteriosclerosis, Chicago. Aaron Kellner, N. Y. Hospital, 525 E. 68th Street, New York 21, N. Y.

ABROAD

July 23-30: International Congress of Radiology, Munich, Germany. H. V. Braunbehrens, Ziemssenstr. 1, Munich 15, Germany.

July 27-30: Shaio Foundation Symposium on Cardiovascular Diseases, Bogota, Colombia. Alberto Vejarano-Laverde, 43-23 Carrera 13, Bogota-Colombia.

September 18-20: International Cardiovascular Society, Munich, Germany. H. Haimovici, 715 Park Avenue, New York 21, N. Y.

September 20-26: Mexican National Institute of Cardiology, International Symposium and Congress, Mexico City. Manuel G. Noguera, National Institute of Cardiology, Av. Cuauhtemoc 300, Mexico, D. F.

LIST OF GRANTS-IN-AID

Following is a list of recipients of Grants-in-Aid awarded by the American Heart Association for the 1959-60 fiscal year, together with the subjects of their studies and the institutions at which these will be conducted.

Continued Grant Awards

George H. Acheson, M.D., University of Cincinnati College of Medicine, Cincinnati. Pharmacological studies of cardiac glycosides and related compounds having saturated lactone rings.

Frederick Aladjem, Ph.D., University of Southern California School of Medicine, Los Angeles. Immunochemical studies on human plasma lipoproteins.

Julian L. Ambrus, M.D., Ph.D., University of Buffalo School of Medicine and Roswell Park Memorial Hospital, Buffalo, N.Y. Therapeutic application of fibrinolytic enzymes.

Franz K. Bauer, M.D., University of Southern California School of Medicine, Los Angeles. Determination of cardiac output by a direct recording technique, using radioiodinated human serum albumin, in patients with myocardial infarctions.

William B. Bean, M.D., State University of Iowa College of Medicine, Iowa City. Lipid metabolism and blood coagulation in atherosclerosis, to support the research of Dr. William E. Connor.

Reinhold Benesch, Ph.D., Marine Biological Laboratory, Woods Hole, Mass. Relationship between chemical structure and diuretic activity in organic mercurials.

Richard J. Bing, M.D., Washington University Medical Service and Veterans Administration Hospital, St. Louis. Cardiac metabolism and contractile proteins of heart muscle.

William S. Blakemore, M.D., University of Pennsylvania School of Medicine, Philadelphia. Evaluation of freeze-dried homografts and synthetic cloth mesh materials used to replace human blood vessels.

Edward H. Bloch, M.D., Ph.D., Western Reserve University School of Medicine, Cleveland. Sequential biophysical analysis of the effect of antigen-antibody reactions on the microcirculation and blood vessel walls in vivo.

Herrman L. Blumgart, M.D., Harvard Medical School at Beth Israel Hospital, Boston. Metabolic aspects of urinary tract infections.

Nancy G. Boucot, M.D., Harvard Medical School, Boston. Alterations in metabolism in renal disease.

Allan J. Brady, Ph.D., University of California Medical Center, Los Angeles. Myocardial tension related to transmembrane potentials and ion fluxes.

Burtis B. Breese, M.D., University of Rochester School of Medicine and Dentistry, Rochester, N.Y. Streptococcal infection in children and their relation to rheumatic fever.

William R. Brewster, Jr., M.D., Massachusetts General Hospital, Boston. Mechanism of action of epinephrine, norepinephrine, the thyroid hormones and adrenal cortical steroids in effecting transfer and utilization of energy for contraction and relaxation of heart muscle.

Nancy M. Buckley, M.D., Albert Einstein College of Medicine of Yeshiva University, New York, N.Y. Cardiodynamics in valve disorders.

Vernon H. Cheldelin, Ph.D., Oregon State College, Corvallis. Oxidative patterns and electron transport in heart muscle.

Hadley L. Conn, Jr., M.D., Hospital of the University of Pennsylvania, Philadelphia. Blood flow and myocardial metabolism with the aid of radioisotope techniques.

William E. Connor, M.D., State University of Iowa College of Medicine, Iowa City. Effect of estrogens upon blood coagulation in men and women; its possible relationship to atherosclerosis.

Loyal L. Conrad, M.D., Veterans Administration Hospital, Oklahoma City, Okla. Activation of the free wall of the right ventricle in the presence of right ventricular hypertrophy and right bundle branch block.

A. W. B. Cunningham, M.B., Ch.B., University of Texas Medical Branch, Galveston. Chemical exchanges in heart tissue culture.

R. Duncan Dallam, Ph.D., University of Louisville School of Medicine, Louisville. Thyroxine and oxidative phosphorylation.

Clarence Dennis, M.D., Ph.D., State University of New York Downstate Medical Center, Kings County Hospital, Brooklyn, N.Y. Use of the heart-lung machine in cases of myocardial infarction in intractable shock.

John R. Derrick, M.D., University of Texas Medical Branch, Galveston. Formulation of the symptom complex, pathology and treatment of mesenteric artery insufficiency.

Richard A. DeWall, M.D., University of Minnesota Medical School, Minneapolis. Perfusion techniques for reparative open intracardiac surgery.

Lewis Dexter, M.D., Peter Bent Brigham Hospital, Boston. Clinical and physiological correlations in valvular regurgitation.

Douglas R. Drury, M.D., University of Southern California School of Medicine, Los Angeles. Observations and experimental studies on rabbits with inherited hypertension.

Isidore S. Edelman, M.D., University of California Medical Center, San Francisco. Relationships among serum pH, serum K+ concentration and total exchangeable potassium and their influences on cardiac dynamics.

H. E. Ederstrom, Ph.D., University of North Dakota School of Medicine, Grand Forks, N.D. Comparative study of the reactivity of blood vessels.

Harold B. Eiber, M.D., New York Medical College, New York, N.Y. Physiological action of heparin.

J. Russell Elkinton, M.D., University of Pennsylvania School of Medicine, Philadelphia. Two grants: Clinical, physiological and biochemical studies of renal failure. Also, supra-optico-hypophyseal system in the cat pertaining to volume and concentration regulation; an effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease.

Franklin H. Epstein, M.D., Yale University School of Medicine, New Haven. Factors influencing renal concentrating ability.

Frank A. Finnerty, Jr., M.D., District of Columbia General Hospital, Washington, D.C.: Pathogenesis of post-partum hypertension.

Alfred P. Fishman, M.D., Columbia University College of Physicians and Surgeons and Presbyterian Hospital, New York, N.Y. Interrelations between respiration and circulation in man.

Ernest C. Foulkes, Ph.D., May Institute for Medical Research of the Jewish Hospital Association, Cincinnati. Control of intracellular electrolyte composition.

Meyer Friedman, M.D., Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco. Further studies concerning the metabolism of cholesterol.

Gerhard H. Giebisch, M.D., Cornell University Medical College, New York, N.Y. Ion transport across renal tubules of the amphibian and mammalian kidney utilizing micropuncture and microelectrode techniques.

Robert P. Gilbert, M.D., Northwestern University Medical School, Evanston, Ill. Hemodynamics of endotoxin shock with special reference to its pathogenesis in monkeys and in man.

Harold D. Green, M.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N.C. Mechanism of and significance of epinephrine dilation (epinephrine reversal) in skeletal muscle, mesenteric and splenic arterial vascular beds.

Jack P. Green, Ph.D., M.D., Yale University School of Medicine, New Haven. Mechanism of action of dicoumarol and vitamin K_1. Also, study of the formation of heparin, histamine and 5-hydroxytryptamine.

Santiago Grisolia, M.D., University of Kansas Medical Center, Kansas City. Metabolism of phosphoglycerate.

Arthur C. Guyton, M.D., University of Mississippi Medical Center, Jackson. Further development and utilization of continuous recording of cardiac output by the Fick prinicple.

E. Raymond Hall, Ph.D., University of Kansas, Lawrence. Cardiovascular disease in free-living mammals other than man, correlated with habits, habitat and heritage.

Calvin Hanna, Ph.D., University of Vermont College of Medicine, Burlington. Tachyphylaxis.

K. Albert Harden, M.D., Howard University College of Medicine, Washington, D.C.: Pulmonary and cardiac dynamics in chronic pulmonary disease.

Tinsley R. Harrison, M.D., Medical College of Alabama, Birmingham. Velocity and acceleration pressure pulses and correlation with other hemodynamic data in the human subject.

D. Mark Hegsted, Ph.D., Harvard University School of Public Health, Boston. Role of magnesium in atherosclerosis.

Milton Helpern, M.D., Office of Chief Medical Examiner, City of New York. Pathological findings in cases of sudden and unexpected death from occlusive coronary artery disease. Correlation of findings with circumstances.

Walter Heymann, M.D., Western Reserve University School of Medicine, Cleveland. Regulation of blood lipid concentration with special reference to pathogenesis of nephrotic hyperlipemia.

John B. Hickam, M.D., Indiana University Medical Center, Indianapolis. Effect of congestive heart failure on pulmonary function in patients with lung disease.

Robert M. Hill, Ph.D., University of Colorado School of Medicine, Denver. Myocardial chromoproteins and their derivatives as indicators of myocardial infarction.

James G. Hilton, M.D., St. Luke's Hospital, New York, N.Y. Adrenal gland physiology.

Hebbel E. Hoff, Ph.D., M.D., and *Russell A. Huggins, Ph.D.*, Baylor University College of Medicine, Houston. Dynamic and electrical analysis of the electrocardiographic changes produced by potassium intoxication.

Walter Hollander, Jr., M.D., University of North Carolina School of Medicine, Chapel Hill. Action of antidiuretic hormone.

Ralph T. Holman, Ph.D., University of Minnesota Medical School, Minneapolis. Polyunsaturated acids and the transport of lipids.

Roger W. Jeanloz, Ph.D., Massachusetts General Hospital, Boston. Chemistry and biochemistry of heparins.

Howard A. Joos, M.D., Children's Hospital Society of Los Angeles, Los Angeles, Calif. Vascular physiology in infancy and childhood.

Manfred L. Karnovsky, Ph.D., Harvard Medical School, Boston. Polyene fatty acids in the adrenal gland, plasma lipoproteins and nervous tissue

Louis N. Katz, M.D., Medical Research Institute, Michael Reese Hospital, Chicago. Metabolic and hemodynamic interrelationships in the intact myocardium.

F. E. Kelsey, Ph.D., University of South Dakota School of Medicine, Vermillion. Mechanism of action of digitoxin and relationed substances.

Ancel Keys, Ph.D., University of Minnesota, Minneapolis. Two grants: Frequency of ischemic heart disease, the cholesterol-lipoprotein system and the habitual diets of populations. Also, effect of diet on blood serum cholesterol and lipoproteins in man, to support the project of Dr. Francisco Grande.

William J. Kuhns, M.D., University of Pittsburgh School of Medicine. Immunochemical studies of human diphtheria antitoxins—investigation of toxin-antitoxin complexes.

Peter T. Kuo, M.D., University of Pennsylvania School of Medicine, Philadelphia. Investigation of vascular fluid dynamics and their influence upon intravascular distribution of plasma lipids and atherosclerosis.

Milton Landowne, M.D., Levindale Hebrew Home and Infirmary, Baltimore. Pathophysiology of aortic and peripheral vascular disorders.

Abel A. Lazzarini, Jr., M.D., New York University Post-Graduate Medical School, New York, N.Y. Metabolic and immunological changes occurring in transplanted tissues.

Alexander Leaf, M.D., Massachusetts General Hospital, Boston. Renal acidifying mechanisms.

David H. Lewis, M.D., Philadelphia General Hospital. Application of underwater acoustics to the diagnosis of heart disease.

F. John Lewis, M.D., Ph.D., Northwestern University Medical School, Chicago. New membrane oxygenator for cardiopulmonary bypass.

Averill A. Liebow, M.D., Yale University School of Medicine, New Haven. Quantitative comparative studies of experimentally induced collateral circulation to the heart.

Lawrence S. Lilienfield, M.D., Ph.D., Georgetown University Medical Center, Washington, D.C. Intrarenal circulation.

William D. Lotspeich, M.D., University of Rochester School of Medicine and Dentistry, Rochester, N.Y. Relation between kidney metabolism and several of its excretory functions.

W. O. Lundberg, Ph.D., Hormel Institute, Graduate School of the University of Minnesota, Austin. Fat metabolism in relation to atherogenesis.

Richard A. MacDonald, M.D., Mallory Institute of Pathology, Boston City Hospital. Role of serotonin in cardiovascular and renal disease.

Martin B. Mathews, Ph.D., LaRabida-University of Chicago Institute, University of Chicago. Macromolecular structure and interactions of connective tissue ground substance.

James W. McCubbin, M.D., Cleveland Clinic. Neural mechanisms in experimental renal hypertension.

Henry C. McGill, Jr., M.D., Louisiana State University School of Medicine, New Orleans. Electron microscopy of vascular lesions.

Henry D. McIntosh, M.D., Duke University School of Medicine, Durham, N.C. Reversibility of increased pulmonary vascular resistance.

Victor A. McKusick, M.D., Johns Hopkins Hospital, Baltimore. Follow-up and extension of the family studies of Raymond Pearl.

John W. Mehl, Ph.D., University of Southern California School of Medicine, Los Angeles. Nutritional and metabolic studies on essential fatty acids, to support the research of Dr. Rosyln B. Alfin-Slater.

Gordon Meiklejohn, M.D., University of Colorado School of Medicine, Denver. Fibrinolytic enzymes, to support the research of Dr. Kurt von Kaulla.

Edward Meilman, M.D., Long Island Jewish Hospital, New Hyde Park, N.Y. Isolation and properties of structural proteins in smooth muscle.

Milton Mendlowitz, M.D., Mount Sinai Hospital, New York, N.Y. Digital circulation in hypertension.

Lewis C. Mills, M.D., Hahnemann Medical College and Hospital, Philadelphia. Renal action of digoxin; effects on steroid and electrolyte excretion.

Gordon K. Moe, M.D., Ph.D., State University of New York Upstate Medical Center, Syracuse. Nature of atrial fibrillation.

Wilfried F. H. M. Mommaerts, Ph.D., University of California Medical Center, Los Angeles. Biophysical aspects of cradiac activity.

A. Vernon Montgomery, Jr., M.D., Ph.D., University

of Colorado School of Medicine, Denver. Genesis and control of ventricular fibrillation.

Margaret G. Morehouse, Ph.D., University of Southern California School of Medicine, Los Angeles. Distribution, synthesis and utilization of heart lipids under normal and pathological conditions.

Peter V. Moulder, M.D., University of Chicago School of Medicine. Chemical and physiological studies on the transplanted canine heart.

Russell M. Nelson, M.D., Ph.D., University of Utah College of Medicine, Salt Lake City. Method for the determination of blood loss during surgical procedures, employing "washed field" techniques.

Jan Nyboer, D.Sc., M.D., Harper Hospital, Detroit. Adaptation of an aperiodic frictionless suspension for study of cardiorespiratory ballistics.

Robert E. Olson, M.D., University of Pittsburgh Graduate School of Public Health. Effect of congestive heart failure due to valvular disease upon the contractile proteins in dogs and man.

Jacques Padawer, Ph.D., Albert Einstein College of Medicine of Yeshiva University, New York, N.Y. Physiology and biochemistry of the mast cell in relation to cardiovascular function and disease.

Charles R. Park, M.D., Vanderbilt University School of Medicine, Nashville, Tenn. Relationship of growth hormone to carbohydrate metabolism and glucose transport in the isolated heart.

Oglesby Paul, M.D., Presbyterian-St. Luke's Hospital, Chicago. Longitudinal study of coronary heart disease.

Gerald B. Phillips, M.D., Columbia University College of Physicians and Surgeons, New York. Individual phospholipids of human serum.

Laurence O. Pilgeram, Ph.D., St. Barnabas Hospital, University of Minnesota Medical School, Minneapolis. Biochemistry of arteriosclerosis.

Hubert V. Pipberger, M.D., Georgetown University Medical Center, Washington D.C. Orthogonal vectorcardiography and electrocardiography.

Calvin H. Plimpton, M.D., American University of Beirut School of Medicine, Beirut, Lebanon. Rheumatic and congenital heart diseases in the Middle East, to support the research of Dr. George A. Rubeiz.

Robert G. Pontius, M.D., Children's Hospital of Pittsburgh. Cardiac metabolism in humans related to extracorporeal circulation.

Jack A. Pritchard, M.D., University of Texas Southwestern Medical School, Dallas. Acquired alterations of the hemostatic mechanism during pregnancy.

Kurt R. Reissmann, M.D., University of Kansas Medical Center, Kansas City. Quantitative relationship of tissue hypoxia and cellular impairment.

Herbert S. Rhinesmith, Ph.D. Allegheny College, Meadville, Pa. Chains in normal adult human hemoglobin; separation and amino acid sequence.

Jonas E. Richmond, Ph.D., Harvard Medical School, Boston. Role of the prosthetic group of proteins in the biosynthesis and metabolism of conjugated proteins.

Lloyd S. Rogers, M.D., State University of New York Upstate Medical Center, Syracuse. Electropolarographic studies of myocardial oxygenation. I. Evaluation of the effect of the Beck I operation on myocardial oxygenation following coronary occlusion in the dog.

Ray H. Rosenman, M.D., Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco. Mechanism of hypercholesteremia and hyperlipemia in experimental nephrosis in rats.

Robert F. Rushmer, M.D., University of Washington School of Medicine, Seattle. Distribution of blood flow in intact dogs.

David D. Rutstein, M.D., Harvard Medical School, Boston. Factors affecting lipoid deposition in human aortic cells in tissue culture.

Peter F. Salisbury, M.D., Ph.D., Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles. Pulmonary edema: Factors which influence its development and regression in the anesthetized dog.

Allen M. Scher, Ph.D., University of Washington School of Medicine, Seattle. Body surface potentials produced by an intracardiac dipole.

Bodil Schmidt-Nielson, Ph.D., Duke University, Durham, N.C. Renal mechanism for urea and salt excretion.

William B. Schwartz, M.D., New England Center Hospital, Boston. Renal regulation of acid-base equilibrium.

Richard S. Schweet, Ph.D., City of Hope Medical Center, Duarte, Cal. Intermediate stages of protein synthesis.

Alvin L. Sellers, M.D., Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles. Metabolic studies on the isolated perfused mammalian kidney.

Alvin P. Shapiro, M.D., University of Pittsburgh School of Medicine. Relationship of hypertensive vascular disease and experimental chronic pyelonephritis.

John T. Sharp, M.D., University of Buffalo School of Medicine, Buffalo, N.Y. Mechanical properties of the lungs in pulmonary edema.

Herbert O. Sieker, M.D., Duke University School of Medicine and Veterans Administration Hospital, Durham, N.C. Cardiopulmonary function in obesity.

Thomas P. Singer, Ph.D., Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit. Electron transport mechanisms in heart and other tissues.

Howard D. Sirak, M.D., and *Walter L. Starkey, Ph.D.*, Ohio State University College of Medicine, Columbus. Development of prosthetic valves for the human heart.

Merrill P. Spencer, M.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N.C. Direct measurement of blood flow in humans.

Mario Stefanini, M.D., St. Elizabeth's Hospital, Boston. Development and evaluation of substances with direct and indirect fibrinolytic activity in vivo for the control of venous and arterial thromboembolism.

Chandler A. Stetson, Jr., M.D., New York University College of Medicine, New York. Participation of the coagulation mechanism in immunological events.

Henry Swan, M.D., University of Colorado School of Medicine, Denver. Physiological and technical studies relating to cardiovascular surgery.

Roy C. Swan, M.D., Cornell University Medical College, New York. Cation transport across cell membranes of skeletal muscle.

Leon Swell, Ph.D., Veterans Administration Center, Martinsburg, Va. Cholesterol metabolism: Mechanism of absorption and regulation in the blood.

Albert Szent-Gyorgyi, M.D., Ph.D., Institute for Muscle Research, Woods Hole, Mass. Chemical macromolecular and histological structure of muscle and chemistry of contraction cycle; mechanochemical coupling.

Helen B. Taussig, M.D., Harriet Lane Home, Johns Hopkins Hospital, Baltimore. Etiology of congenital malformations of the heart and great vessels.

Henry L. Taylor, Ph.D., University of Minnesota School of Public Health, Minneapolis. Death rates and physical activity among railroad workers with special reference to coronary heart disease in middle-aged men.

Louis Tobian, Jr., M.D., University of Minnesota Medical School, Minneapolis. Physiology of hypertension and the renal anti-hypertensive mechanism in man and experimental animals.

Richard W. Von Korff, Ph.D., University of Minnesota Medical School, Minneapolis. Investigations on the chemical nature of fibrinogen, fibrin and fibrinopeptide.

Sheppard M. Walker, Ph.D., University of Louisville School of Medicine. Effect of electric current and certain metabolites on cardiac automaticity.

Homer R. Warner, M.D., Ph.D., University of Utah College of Medicine and Latter-Day Saints Hospital, Salt Lake City. Influence of changes in peripheral resistance and posture on backflow in the aorta of patients with aortic insufficiency.

James V. Warren, M.D., University of Texas School of Medicine, Galveston. Determinants of cardiac output in man.

Levin L. Waters, M.D., Yale University School of Medicine, New Haven, Conn. Modification of the lesions of experimental atherosclerosis.

Sigmund A. Wesolowski, M.D., State University of New York Downstate Medical Center and Kings county Hospital, Brooklyn, N.Y. Development and application of a test to determine the blood flow to a given local part.

Stanford Wessler, M.D., Harvard Medical School at Beth Israel Hospital, Boston. Intravascular thrombosis.

Walter S. Wilde, Ph.D., University of Michigan Medical School, Ann Arbor. Localization of nephron transport by stop flow analysis.

C. M. Wilhelmj, M.D., Creighton University School of Medicine, Omaha. Neuro-hormonal factors in hypertension.

Charles F. Wilkinson, Jr., M.D., New York University Post-Graduate Medical School, New York. Genetic and metabolic study of familial hyperlipemia.

Peter N. Witt, M.D., Research Foundation of State University of New York, Syracuse. Investigation of the mechanism of action of drugs with positive inotropic effect on the heart with particular regard to their effect on ion movements.

Harry Y. C. Wong, Ph.D., Howard University College of Medicine, Washington, D.C. Role of exercise and endocrine glands in the alteration of blood cholesterol, phospholipids and lipoproteins in relation to atherosclerosis.

New Approved Grants

Bernard C. Abbott, Ph.D., University of California, Los Angeles. I. Nature of cardiac automatism. II. Muscle nucleic acid and its possible participation in muscular contraction. III. "High energy" phosphate compounds in muscle of different zoological groups.

Gerald S. Berenson, M.D., Louisiana State University School of Medicine, New Orleans. Effect of inflammation on connective tissue.

Herrman L. Blumgart, M.D., Harvard Medical School at Beth Israel Hospital, Boston. Pathogenesis of intravascular thrombosis, to support the research of Dr. Stanford Wessler.

David F. Bohr, M.D., University of Michigan Medical School, Ann Arbor. Determinants of non-neurogenic vascular tone in normal and hypertensive animals.

Walter M. Booker, Ph.D., Howard University College of Medicine, Washington, D.C. Effect of some cardiac drugs on the heart during normothermia and hypothermia. Influence of cortisone and its congeners on heart action.

Edwin Boyle, Jr., M.D., Medical College of South Carolina, Charleston. Significance of intravascular aggultination of blood cells on microcirculation.

J. H. U. Brown, Ph.D., Emory University School of Medicine, Atlanta. Metabolism of steroids in heart and kidney.

Robert B. Case, M.D., St. Luke's Hospital, New York. Determination of coronary flow using a radioactive gas.

James H. Casey, M.D., Ph.D., Marquette University School of Medicine, Milwaukee. Evaluation of factors influencing the hemodynamics of effective perfusion in extracorporeal circulation.

Glen G. Cayler, M.D., University of Oklahoma Medical School, Oklahoma City. Longitudinal study of hemodynamic and pulmonary vascular changes in the full-term and premature puppy.

Thomas B. Clarkson, D.V.M., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N.C. Chemotherapeutic studies on pigeon atherosclerosis.

Ernest Craige, M.D., University of North Carolina School of Medicine, Chapel Hill. Left atrial pressure and pulmonary hypertension in patent ductus arteriosus.

T. S. Donowski, M.D., University of Pittsburgh School of Medicine. Application and assessment of hemodialysis and other forms of treatment in clinical and experimental renal insufficiency and the cardiovascular effects of such procedures, to support the research of Dr. Frank Mateer.

Thomas D. Darby, Ph.D., Medical College of South Carolina, Charleston. Relations between acute cardiac failure, shock and acid-base rearrangements.

Peter E. Dressel, Ph.D., University of Manitoba Faculty of Medicine, Winnipeg, Canada: Automaticity in isolated preparations of cardiac muscle.

David H. Elwyn, Ph.D., Harvard Medicine School, Boston. Relations between amino acid intake, tissue amino acid levels and turn-over, and the rates of biosynthesis of proteins.

Daniel M. Enerson, M.D., State University of New York Upstate Medical Center, Syracuse. Hepatic blood flow and metabolism during extracorporeal circulation with the mechanical pump-oxygenator.

George Fawaz, Ph.D., M.D., American University of Beirut School of Medicine, Beirut, Lebanon. Effect of arrythmias on the performance and metabolism of the isolated mammalian heart (heart-lung preparation).

Francis F. Foldes, M.D., Mercy Hospital, Pittsburgh. Circulatory effects of narcotic analgesics in man.

Ernst K. Franke, Dr. Ing., University of Cincinnati and Cincinnati General Hospital. Peripheral circulation in health and disease by means of calorimetric methods.

Melvin J. Fregly, Ph.D., University of Florida College of Medicine, Gainesville. Regulation of sodium intake by hypertensive rats.

Jacques R. Fresco, Ph.D., Harvard University, Cambridge, Mass. Macromolecular structure of enzymatically synthesized polynucleotides in relation to nucleic acid structure and function.

Robert H. Furman M.D., Oklahoma Medical Research Foundation, Oklahoma City. Relative resistance of human serum lipoprotein fractions to destruction by physical forces.

John H. Gibbon, Jr., M.D., Jefferson Medical College of Philadephia. Physiological study of myocardial changes in induced cardiac arrest.

David M. Gibson, M.D., Indiana University Medical School, Indianapolis. Role of biotin in the biosynthesis of fatty acids.

Robert P. Glover, M.D., Presbyterian Hospital, Philadelphia. Experimental evaluation of surgical methods for treatment of coronary insufficiency.

Robert A. Good, M.D., Ph.D., University of Minnesota Medical School, Minneapolis. Continued study of basic mechanisms involved in pathogenesis of rheumatic fever and other cardiovascular-renal diseases.

Allan V. N. Goodyer, M.D., Yale University School of Medicine, New Haven, Conn. Extracardiac determinants of ventricular competence and myocardial metabolism in the intact animal.

Carl W. Gottschalk, M.D., University of North Carolina School of Medicine, Chapel Hill. Micropuncture study of kidney function.

Robert D. Griesemer, M.D., Massachusetts General Hospital, Boston. Lipid metabolism in the skin.

Robert E. Gross, M.D., Children's Hospital, Boston. Studies relevant to surgical treatment of congenital heart disease.

Lucien B. Guze, M.D., University of California at Los Angeles School of Medicine. Observations on the association of hypertension and experimental pyelonephritis.

Richard J. Havel, M.D., University of California School of Medicine, San Francisco. Mechanisms and control of fatty acid transport and metabolism.

Edward W. Hawthorne, M.D., Ph.D., Howard University College of Medicine, Washington, D.C. Experimental hypertension: Part IV—Continuous and semicontinuous remote monitoring of the instantaneous changes in arterial pressure in dogs and primates developing experimental hypertension.

Emanuel C. Hertzler, Ph.D., Kent State University, Kent, Ohio. Serotonin, blocking agents and transmission in sympathetic ganglia.

Robert Hill, Ph.D., University of California, Berkeley. Dietary control of hepatic and arterial lipid metabolism.

Kurt Hirschhorn, M.D., New York University Post-Graduate Medical School. Incidence of essential hyperlipemia and essential familial hypercholesterolemia in the United States.

Brian F. Hoffman, M.D., State University of New York Downstate Medical Center, Brooklyn, N.Y. Electrophysiology of cardiac muscle.

William C. Holland, M.D., University of Mississippi Medical Center, Jackson. Mode of action of antiarrhythmic agents.

Edward W. Hook, M.D., Johns Hopkins University

School of Medicine, Baltimore. Host factors in experimental streptococcal infection.

John M. Howard, M.D., Hahnemann Medical College and Hospital, Philadelphia. Anatomy and function of normal and pathological lymph vessels by radiographic and isotopic techniques.

Alan J. Johnson, M.D., New York University Bellevue Medical Center. Enzyme studies and coagulation research.

Nathan O. Kaplan, Ph.D., Brandeis University, Waltham, Mass. Metabolic significance of nucleotides in cardiovascular tissue.

Samuel Kaplan, M.D., Children's Hospital Research Foundation, Cincinnati. Myocardial oxygen tension.

Yale J. Katz, Ph.D., M.D., University of Southern California School of Medicine, Los Angeles. Augmentation of kidney function by revascularization of the kidney.

Grace P. Kerby, M.D., Duke University School of Medicine, Durham, N.C. Metabolism of acid mucopolysaccharides of ground substance.

Charles E. Kossmann, M.D., New York University college of Medicine. Correlation of intracellular potentials of single cardiac fibers with mechanical function.

Otto Krayer, M.D., Harvard Medical School, Boston. Further studies on the circulatory action of the Rauwolfia alkaloids.

Hiroshi Kuida, M.D., University of Utah College of Medicine, Salt Lake City. Pressure-volume relationships of the pulmonary circulation; the significance of the left atrial-pulmonary venous system as a volume receptor.

Frank S. LaBella, Ph.D., University of Manitoba Faculty of Medicine, Winnipeg, Canada. Biochemistry of elastic tissue.

John S. LaDue, M.D., Ph.D., Sloan-Kettering Institute for Cancer Research, New York. Electrocardiogram during physical exercise.

Christian J. Lambertsen, M.D., University of Pennsylvania School of Medicine, Philadelphia. Physiology and pharmacology of the coronary circulation with special reference to intracoronary reflexes and their relation to myocardial metabolism.

Willoughby Lathem, M.D., University of Pittsburgh School of Medicine, Pittsburgh. Mechanism of proteinuria and characterization of the glomerular membrane defect in renal disease.

Louis Leiter, M.D., Ph.D., Montefiore Hospital, New York. Role of body electrolyte content in the response to drug therapy of hypertension.

Robert S. Levy, Ph.D., University of Louisville School of Medicine. Enzymatic activity on natural and synthetic substrates of lipoprotein lipase from tissue and plasma.

Robert A. Liebelt, Ph.D., M.D., Baylor University College of Medicine, Houston. Effect of the adrenal gland on obesity in mice.

J. Maxwell Little, Ph.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N.C. Relationships between mixed venous pO_2 and adrenal cortical activity and cardiodynamics.

Robert C. Little, M.D., Seton Hall College of Medicine and Dentistry, Jersey City, N.J. Effect of variable right ventricular stress on the dynamics of the left ventricle.

Daniel S. Lukas, M.D., Cornell University Medical College, New York, N.Y. Quantitation of valvular regurgitation.

Samuel Mallov, Ph.D., Research Foundation of State University of New York, Syracuse. Tissue lipoprotein lipase.

H. S. Mayerson, Ph.D., Tulane University School of Medicine, New Orleans. Permeability of lymphatic vessels.

H. C. Meng, M.D., Ph.D., Vanderbilt University School of Medicine, Nashville, Tenn. Production of lipemia clearing factor and its inhibitor and their role in lipid metabolism and atherogenesis.

James Metcalfe, M.D., Boston Lying-in Hospital. Maternal circulation in pregnancy.

Benjamin F. Miller, M.D., May Institute for Medical Research of the Jewish Hospital Association, Cincinnati. Arteriosclerosis in the rat.

William R. Milnor, M.D., Johns Hopkins Hospital, Baltimore. Relationships between pulmonary vascular resistance and pulmonary blood volume.

Hugh Montgomery, M.D., Hospital of the University of Pennsylvania, Philadelphia. Oxygen tension of muscle.

H. Mitchell Perry, Jr., M.D., Washington University School of Medicine, St. Louis. Relation of trace metals to atherosclerosis.

John W. Porter, Ph.D., University of Wisconsin, Madison. Mechanism of the enzymatic synthesis of fatty acids.

Oscar D. Ratnoff, M.D., Western Reserve University School of Medicine, Cleveland. Initiation of blood coagulation.

Simon Rodbard, M.D., Ph.D., University of Buffalo Chronic Disease Research Institute, Buffalo, N.Y. Role of mechanical tension (pressure X radius) in myocardial dynamics.

Edward Ronwin, Ph.D., University of Minnesota College of Pharmacy, Minneapolis. Enzymes involved in blood clotting and their mechanism of action; isolation of indicated clotting reaction intermediates.

Abraham M. Rudolph, M.D., Children's Medical Center, Boston. Pulmonary hypertension in congenital heart disease.

Jay P. Sanford, M.D., University of Texas Southwestern Medical School, Dallas. Relationship of

inapparent pyelonephritis to arterial hypertension.

Philip N. Sawyer, M.D., State University of New York Downstate Medical Center, Brooklyn, N.Y. Bioelectric phenomena and intravascular thrombosis.

Robert C. Schlant, M.D., Emory University School of Medicine, Atlanta. Use of thermistors as flowmeters.

Arthur J. Scaman, M.D., University of Oregon Medical School, Portland. Controlled long-term study of continuous anticoagulant therapy in coronary artery disease.

Alan C. Seigel, M.D., Children's Memorial Hospital, Chicago. Group A streptococcal infections in children, with particular refrence to the attack rate and prevention of rheumatic fever.

Herbert O. Sieker, M.D., Duke University School of Medicine, Durham, N.C. Mechanisms of regulation for the pulmonary circulation, to support the research of Dr. Felice Manfredi.

Marvin D. Siperstein, M.D., Ph.D., University of Texas Southwestern Medical School, Dallas. Factors influencing the excretion and synthesis of cholesterol.

Richard T. Smith, M.D., University of Florida College of Medicine, Gainesville. Ontogeny of inflammatory and immune responses.

Jeremiah Stamler, M.D., Chicago Board of Health. Assessment of ability to prevent clinical coronary heart disease by nutritional means in high-risk middle-aged males.

Thomas E. Starzl, M.D., Northwestern University Medical School, Chicago. I. Surgical therapy of aortic insufficiency. II. Treatment of cerebral edema due to anoxia.

Andrew G. Szent-Gyorgyi, M.D., Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass. Structure of the contractile proteins and chemistry of contraction.

C. Bruce Taylor, M.D., Presbyterian-St. Luke's Hospital, Chicago. Human cholesterol metabolism and its relationship to atherosclerosis.

Sam A. Threefoot, M.D., Touro Infirmary, New Orleans. Direct observation of vascular channels, capillary beds and lymphatics of the intact human male.

Kurt N. von Kaulla, M.D., University of Colorado School of Medicine, Denver. Fibrinolytic enzymes.

William H. Wade, M.D., University of Missouri Medical Center, Columbia. Use of dextran sulfate as an anticoagulant for open-heart surgery.

William B. Wartman, M.D., Northwestern University Medical School, Chicago. Response of endothelial cells to injury.

Cecil J. Watson, M.D., University of Minnesota Medical School, Minneapolis. Fatty acids and atherosclerosis, to support the research of Dr. Naip Tuna.

J. Leyden Webb, Ph.D., University of Southern California School of Medicine, Los Angeles. Two grants, effects of cardioactive drugs on atrial membrane potentials and contractility. Also, effects of metal-chelating agents on atrial fibrillation, to support the research of Dr. William C. Yang.

René Wégria, M.D., Saint Louis University School of Medicine. Coronary circulation and cardiac metabolism under normal and pathological conditions.

Max H. Weil, M.D., Ph.D., University of Southern California School of Medicine, Los Angeles. Effect of head down position on the efficiency of circulation in the presence of shock.

John M. Weller, M.D., University of Michigan Medical School, Ann Arbor. Investigation of abnormalities of electrolyte metabolism in hypertension.

Louis G. Welt, M.D., University of North Carolina School of Medicine, Chapel Hill. Evaluation of the usefulness of extracorporeal hemodialysis in the management of chronic renal insufficiency.

Laurence G. Wesson, Jr., M.D., New York University Post-Graduate Medical School. Mechanisms of sodium chloride excretion.

E.H. Wood, M.D., Ph.D., Mayo Association, Rochester, Minn. Indicator-dilution curves recorded simultaneously from sites upstream and downstream to a regurgitant valve following injections of indicator at various sites into the circulatory system.

Francis C. Wood, M.D., Hospital of the University of Pennsylvania, Philadelphia. Alterations in pressure-volume-flow relationships within the cardiovascular system produced by direct cardiovascular stresses and effect of these alterations on transcapillary kinetics and organ metabolism, to support the research of Dr. Hadley Conn.

Harrison F. Wood, M.D., Irvington House, Irvington-on-Hudson, N.Y. Epidemiological study of methods for prevention of rheumatic fever and rheumatic heart disease.

Robert A. Woodbury, M.D., Ph.D., University of Tennessee Medical Units, Memphis. Mechanism of action of sympathomimetic amines: Blocking action of cholinergic drugs upon adrenergic receptors and the investigation of a previously undescribed mechanism contributing to angina attacks.

Paul N. Yu, M.D., University of Rochester School of Medicine and Dentistry. Determination of blood flow and volume by isotope dilution technique.

Marjorie B. Zucker, Ph.D., Sloan-Kettering Institute for Cancer Research, New York. Platelet agglutination and thrombosis.

Benjamin W. Zweifach, Ph.D., New York University-Bellevue Medical Center. Mechanisms of tissue injury.

CONTRIBUTORS TO THIS ISSUE

MARVIN C. BECKER, M.D.

Chief of the Cardiac Clinic, Beth Israel Hospital, Newark, N. J.

HOWARD B. BURCHELL, M.D., PH.D.

Consultant, Section of Medicine, Mayo Clinic; Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

SIDNEY COHEN, M.D.

Director, Department of Microbiology, Michael Reese Hospital, Chicago, Ill.

DONALD B. EFFLER, M.D.

Associate Professor of Thoracic Surgery and Head of the Department, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

AARON FINKELSTEIN, M.D.

Assistant in the Cardiac Clinic, Beth Israel Hospital, Newark, N. J.

ARTHUR H. GRIEP, M.D.

Formerly, Graduate Student in Cardiovascular Disease, Massachusetts General Hospital, Boston, and Special Trainee in Cardiology, U. S. Veterans Hospital, West Roxbury, Mass.; Presently, Evansville, Ind.

NORMAN JOLLIFFE, M.D.

Director, Bureau of Nutrition, Department of Health, City of New York, N. Y.

EUGENE R. JOLLY, M.D.

Medical Officer, New Drug Branch, U. S. Department of Health, Education, and Welfare, Food and Drug Administration, Washington, D.C.

LAWRENCE J. MCCORMACK, M.S., M.D.

Assistant Professor of Anatomic Pathology, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

CLARK H. MILLIKAN, M.D.

Consultant, Section of Neurology, Mayo Clinic; Associate Professor of Neurology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

KENNETH M. MOSER, M.D.

Instructor in Medicine, Georgetown University Medical School; Director, Enzyme Research Laboratory, District of Columbia General Hospital, Washington, D. C.

WILLIAM L. PROUDFIT, M.D.

Associate Professor of Cardiovascular Disease, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

D. VINCENT PROVENZA, PH.D.

Professor, Department of Histology and Embryology, Baltimore College of Dental Surgery, Dental School, University of Maryland, Baltimore, Md.

EDWIN L. ROTHFELD, M.D.

Public Health Service Research Fellow of the National Health Institute, at Beth Israel Hospital, Newark, N. J.

GEORGE P. SAYRE, M.D., M.S.

Consultant, Section of Pathologic Anatomy, Mayo Clinic; Associate Professor of Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

SIDNEY, SCHERLIS, M.D.

Assistant Professor, Department of Medicine, School of Medicine, University of Maryland, Baltimore, Md.

MILTON SHOSHKES, M.D.

Assistant in the Cardiac Clinic, Beth Israel Hospital, Newark, N. J.

ALLEN SILVERSTEIN, M.D.
U. S. Public Health Service, Assistant Resident in Neurology, The Mount Sinai Hospital, New York, N. Y.

CALVIN SMITH, M.D.
Clinical Assistant in the Cardiac Clinic, Beth Israel Hospital, Newark, N. J.

ISAAC STARR, M.D.
Hartzell Research Professor of Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

H. J. C. SWAN, M.B., M.R.C.P., PH.D.
Consultant, Section of Physiology, Mayo Clinic; Assistant Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

FERNANDO A. TAPIA, M.D.
Special Fellow in Cardiology, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

CAROLINE BEDELL THOMAS, M.D.
Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

F. S. P. VAN BUCHEM, M.D.
Professor of Internal Medicine, University of Groningen; Director of the Internal Department, University Hospital, Groningen, Netherlands.

FRED W. WACHTEL, M.D.
Assistant in the Cardiac Clinic, Beth Israel Hospital, Newark, N. J.

KHALIL G. WAKIM, M.D., PH.D.
Consultant, Section of Physiology, Mayo Clinic; Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

JACK P. WHISNANT, M.D., M.S.
Consultant, Section of Neurology, Mayo Clinic; Instructor in Neurology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

EARL H. WOOD, M.D., PH.D.
Consultant, Section of Physiology, Mayo Clinic; Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

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